

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

Date of mailing (day/month/year) 04 April 2001 (04.04.01)	
International application No. PCT/CA00/00850	Applicant's or agent's file reference 11699-4
International filing date (day/month/year) 21 July 2000 (21.07.00)	Priority date (day/month/year) 21 July 1999 (21.07.99)
Applicant YUDIN, Andrei et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 20 February 2001 (20.02.01)

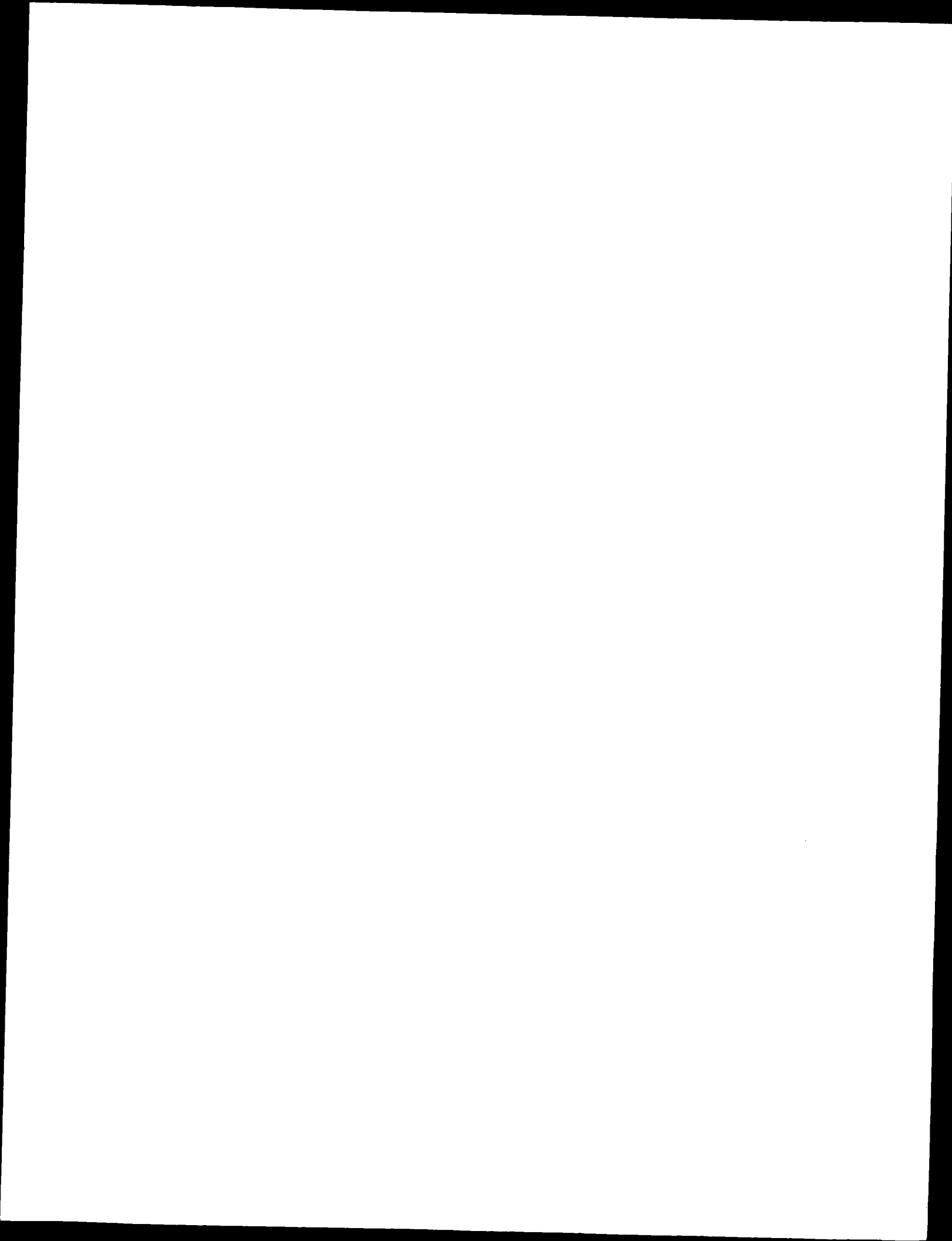
☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>11699-4</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 00/ 00850</b>	International filing date (day/month/year) <b>21/07/2000</b>	(Earliest) Priority Date (day/month/year) <b>21/07/1999</b>
Applicant <b>1428388 ONTARIO LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

#### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

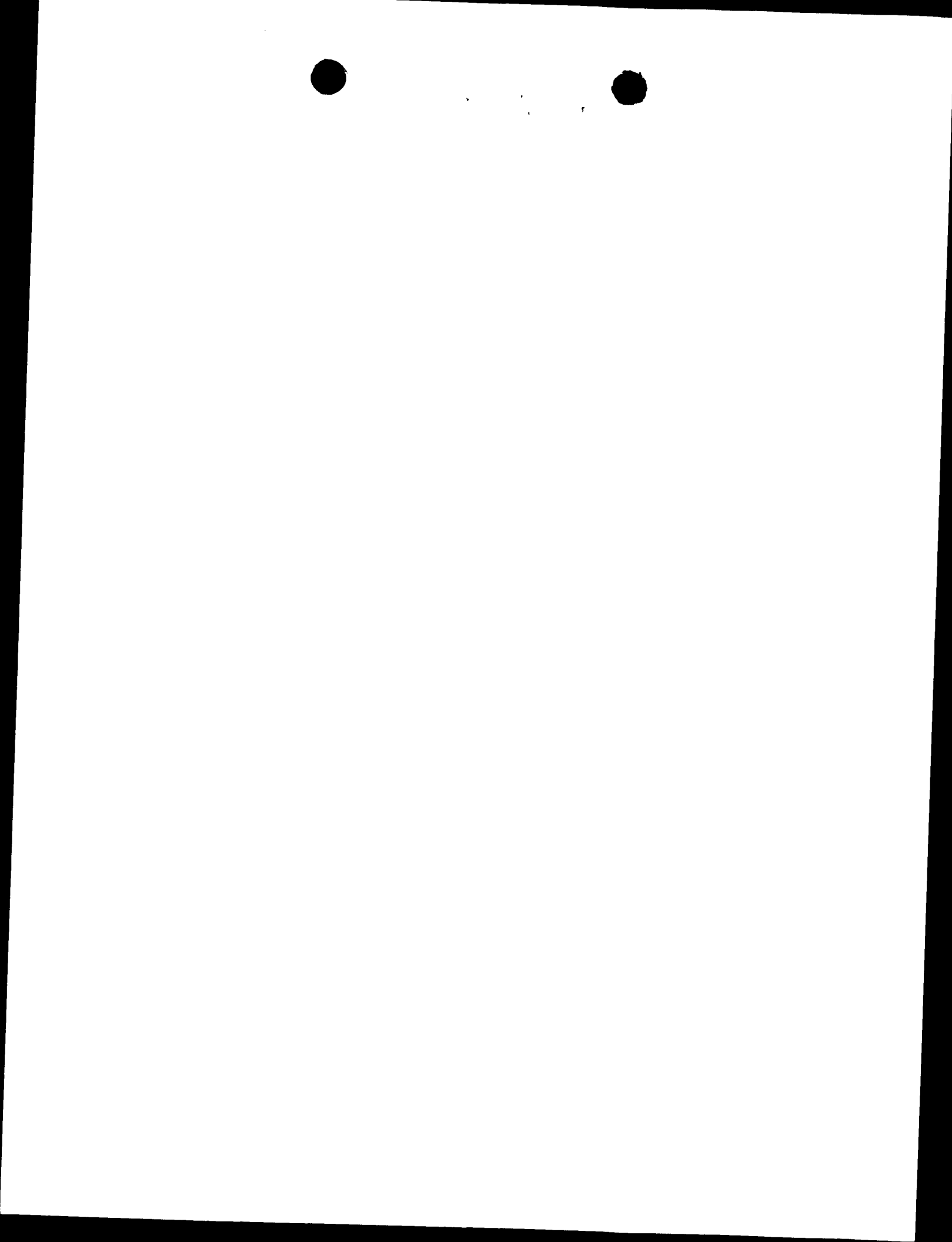
6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.



## INTERNATIONAL SEARCH REPORT

International Application No

P/CA 00/00850

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 C07C39/38 C07C43/225 C07C43/23 C07B53/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>M. T. REETZ:            "3,3'-Dinitrooctahydrobinaphthol: a new            chiral ligand for metal-catalyzed            enantioselective reactions"            TETRAHEDRON LETTERS,            vol. 38, no. 30, 1997, pages 5273-5276,            XP004083296            OXFORD GB            cited in the application            the whole document</p> <p style="text-align: center;">--- -/--</p>	1-9, 27

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

20 July 2001

Date of mailing of the international search report

01/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Wright, M



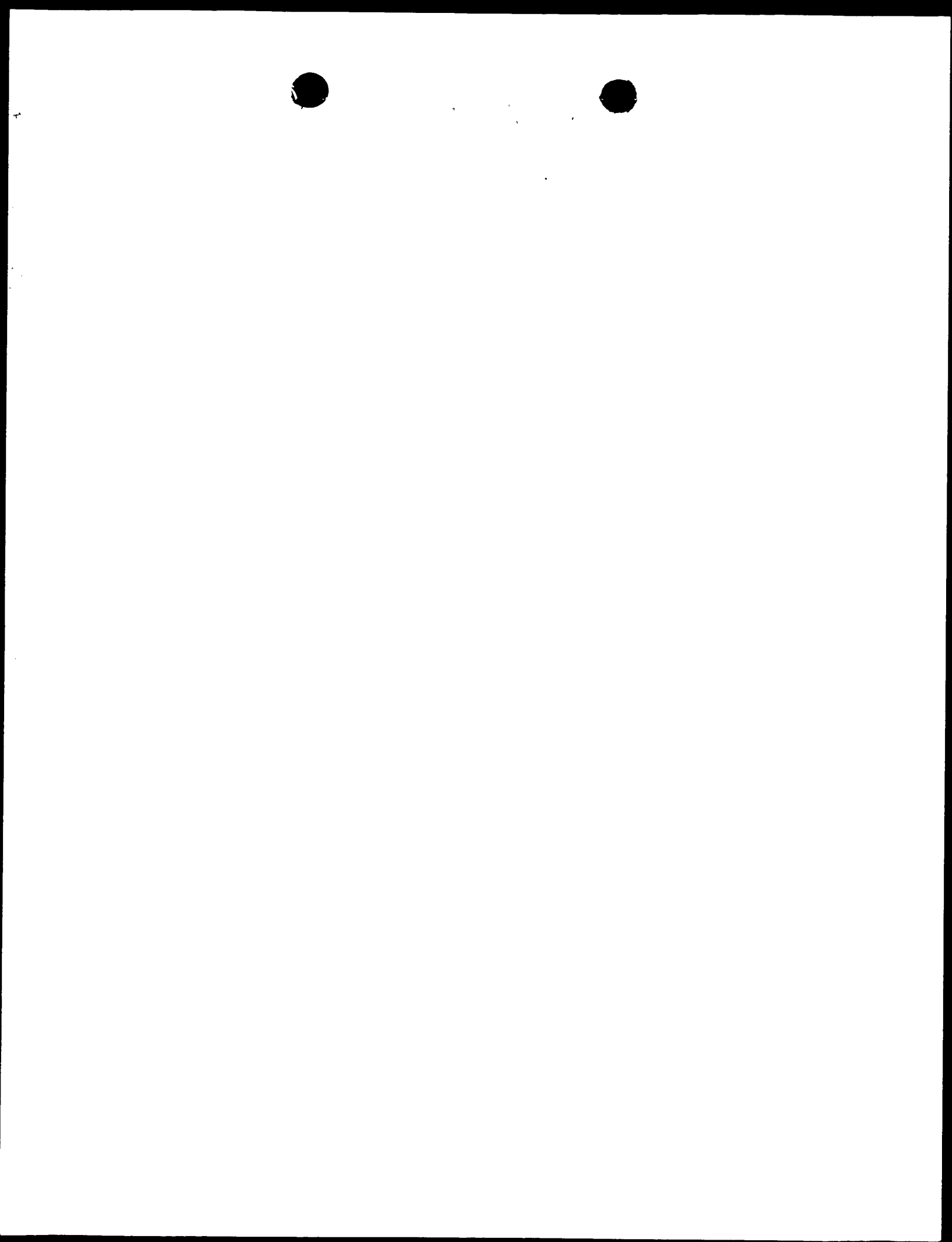
## INTERNATIONAL SEARCH REPORT

International Application No

P/CA 00/00850

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. TERADA: "Diastereoselective and enantioselective glyoxylate-ene reaction catalyzed by a new class of binaphthol-derived titanium complex" TETRAHEDRON LETTERS, vol. 35, no. 36, 1994, pages 6693-6696, XP002172601 OXFORD GB cited in the application the whole document	1-9, 16, 27
X	--- P-A JAFFRÈS: "Phosphonation of 1,1'-binaphthalene-2,2'-diol (BINOL): synthesis of (R)- and (S)-2,2'-dihydroxy-1,1'-binaphthalene-6,6'-diylphosphonic acid" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, 1998, pages 2083-2089, XP002172602 LETCHWORTH GB page 2083 -page 2085	1-8
P,X	--- A. K. YUDIN: "F8BINOL, an electronically perturbed version of BINOL with remarkable configurational stability" ORGANIC LETTERS, vol. 2, no. 1, 2000, pages 41-44, XP002172603 the whole document -----	1-16, 18, 27



101 031449 /

PATENT COOPERATION TREATY

REC'D 15 FEB 2002

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

8

Applicant's or agent's file reference 11699-4	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA00/00850	International filing date (day/month/year) 21/07/2000	Priority date (day/month/year) 21/07/1999
International Patent Classification (IPC) or national classification and IPC C07C39/38		
Applicant <b>1428388 ONTARIO LIMITED</b> (YLEKTRA INC. et al.)		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

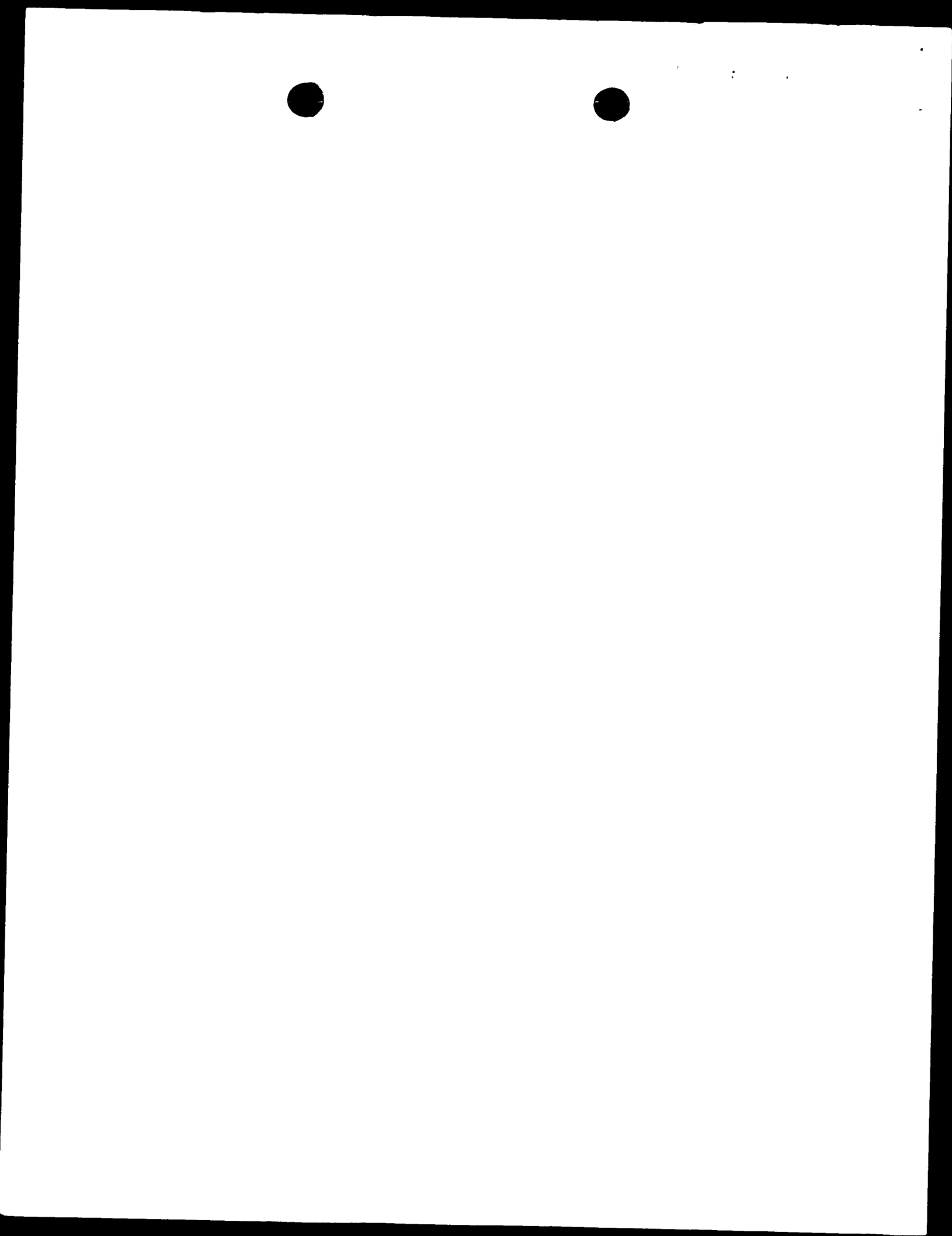
- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  20/02/2001	Date of completion of this report  12. 02. 2002
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer  Wright, M  Telephone No. +31 70 340 3124  



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA00/00850

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-24 as originally filed

**Claims, No.:**

1-50 as received on 12/11/2001 with letter of 01/11/2001

**Drawings, sheets:**

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00850

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	2-23,25-50
	No:	Claims	1,24
Inventive step (IS)	Yes:	Claims	2-23,25-50
	No:	Claims	1,24
Industrial applicability (IA)	Yes:	Claims	1-50
	No:	Claims	

### 2. Citations and explanations see separate sheet



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/CA00/00850

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**  
Tetrahedron: Asymmetry, Vol. 7, No., pp 1883-1886 (D1) and Chem. Abs. 126: 7806w (D2) disclose asymmetric bis(pentafluorophenyl)aminoethanols; D2 discloses their use as catalysts in the asymmetric reduction of ketones. D1 and D2 are therefore novelty-destroying for claims 1 and 24. Since these claims lack novelty there is no basis for the recognition of inventive step.

The subject-matter of claims 2-23 and 25-50 is not disclosed in the prior art.

The use of asymmetric polyfluorinated biphenyl, binaphthyl or bipyridyl compounds as catalysts in asymmetric processes or to generate libraries of asymmetric ligands is not suggested by the prior art.



(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
1 February 2001 (01.02.2001)

PCT

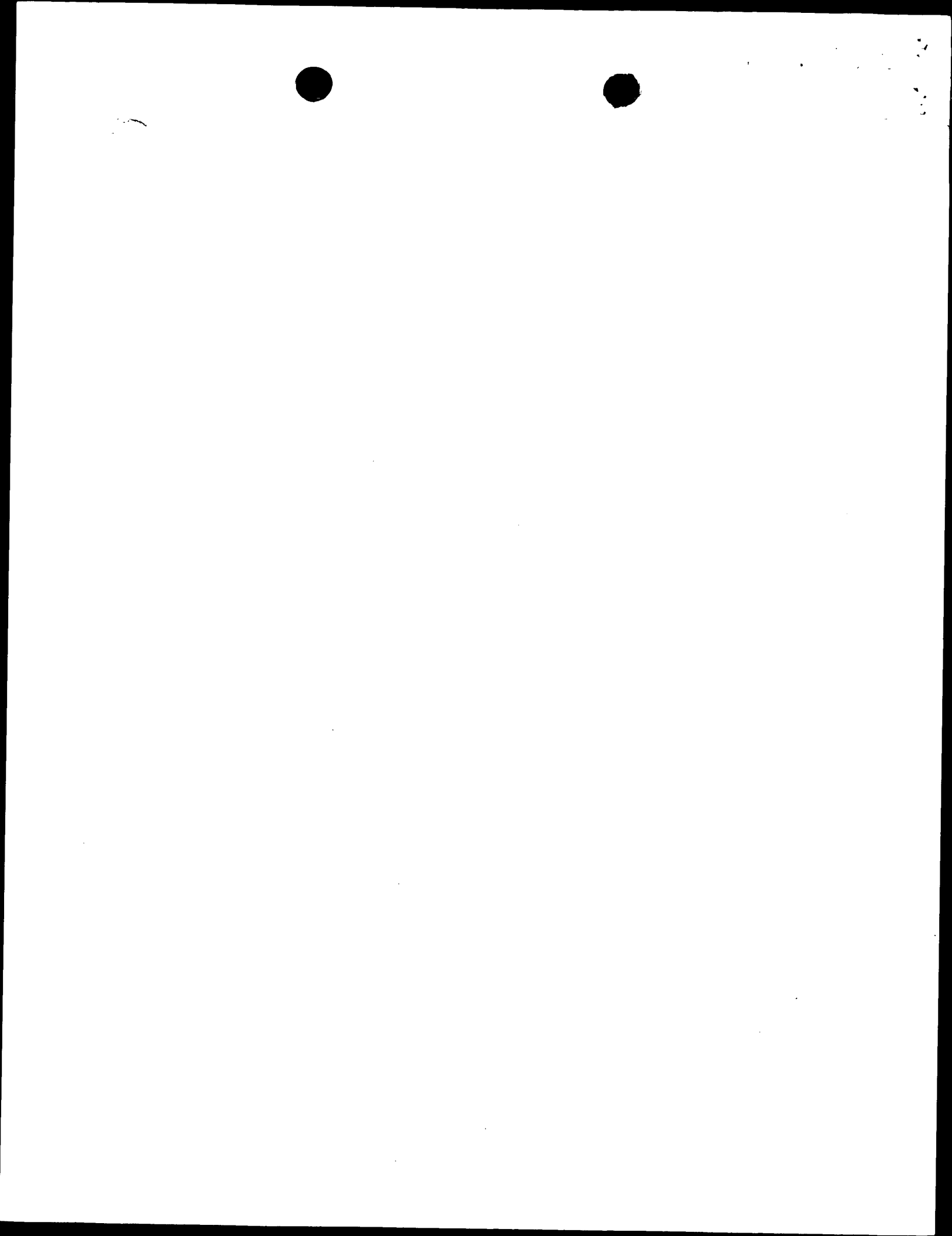
(10) International Publication Number  
**WO 01/07386 A2**

- (51) International Patent Classification<sup>7</sup>: C07C 39/38, 43/225, 43/23, C07B 53/00
- (21) International Application Number: PCT/CA00/00850
- (22) International Filing Date: 21 July 2000 (21.07.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/144,812 21 July 1999 (21.07.1999) US  
60/201,730 4 May 2000 (04.05.2000) US
- (71) Applicant (for all designated States except US): **1428388 ONTARIO LIMITED** [CA/CA]; 30 Humewood Drive, Toronto, Ontario M6C 2W4 (CA).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **YUDIN, Andrei** [CA/CA]; 30 Humewood Drive, Toronto, Ontario M6C 2W4 (CA). **MARTYN, Leo, James, Patrick** [CA/CA]; 3349 Mississauga Road, #165, Mississauga, Ontario L5L 1J7 (CA). **PANDIARAJU, Subramanian** [CA/CA]; 393 Whitmore Avenue, Toronto, Ontario M6E 2N5 (CA).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— Without international search report and to be republished upon receipt of that report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ASYMMETRIC LIGANDS HAVING USE AS CATALYSTS

(57) Abstract: Disclosed are electronically perturbed asymmetric aromatic ligands. In one aspect, the ligands are polyfluorinated. The ligands may be nucleophilically substituted. The ligands have many useful applications including catalytic applications. In a preferred aspect, the ligands are polyfluorinated binaphthyl ring derivatives, which are 2,2' dihydroxy or dialkoxy substituted.

WO 01/07386 A2



1 Title: Asymmetric Ligands Having Use As Catalysts

2

3 RELATED APPLICATION DATA

4 This application claims priority from United States Provisional  
5 Patent Application Nos. 60/144,812 and 60/201,730, filed July 21, 1999 and  
6 May 4, 2000, respectively, the specifications of which are hereby  
7 incorporated by reference in their entirety.

8

9 FIELD OF THE INVENTION

10 The present invention relates to electronically perturbed asymmetric  
11 aromatic ligands. In one aspect it relates to polyfluorinated aromatic  
12 ligand catalysts that may be nucleophilically modified. The ligands may be  
13 used in catalytic processes.

14

15 BACKGROUND OF THE INVENTION

16 Modern asymmetric synthesis often calls for catalytic  
17 transformations. Understanding the balance of steric and electronic  
18 factors is required in order to fine-tune a catalyst to achieve optimal rate  
19 and selectivity in a particular reaction. The analysis of steric  
20 environments around metal centers has traditionally dominated  
21 attempts to explain and predict the outcome of metal-based  
22 enantioselective processes. In comparison, the importance of electronic  
23 effects in asymmetric induction was appreciated only in recent years.  
24 Several known catalytic systems employ electronically diverse  
25 substituents on ligands in order to modulate reactivity of the metal  
26 center.

27 For example, in the catalytic asymmetric epoxidation of  
28 unfunctionalized olefins, electronic properties of substituents on chiral  
29 *salen* ligands determine the nature of transition state (M. Palucki et al *J.*  
30 *Am. Chem. Soc.* 1998, 120, 948). The later transition state leads to higher  
31 enantioselectivities and electronic attenuation of electrophilic Mn=O

1 centers affords higher levels of enantiomeric excess. Enhancement of  
2 enantioselectivity through incorporation of fluorine atoms on chiral  
3 phosphine ligands in the asymmetric hydrocyanation of olefins was  
4 documented (T.V. Rajanbabu, A.L. Casalnuovo *J. Am. Chem. Soc.* 1996,  
5 118, 6325). The concept of induced electronic asymmetry allows one to  
6 increase the enantioselectivity of rhodium-catalyzed hydroboration of  
7 olefins (A. Schnyder et al. *Angew Chem. Int. Ed. Engl.* 1995, 34, 931).

8 Much research has been devoted to the development of chiral  
9 ligands. Among these, the 2,2'-dihydroxy-1,1'-binaphthyl ("BINOL") and  
10 related molecules with axial chirality have found wide utility in  
11 asymmetric catalysis. Over the years, several modifications to the BINOL  
12 skeleton aimed at modifying its steric and electronic properties have been  
13 reported. For example, partially hydrogenated BINOL was used as a  
14 catalyst precursor in enantioselective alkylation of aldehydes (A.S.C.  
15 Chan et al. *J. Am. Chem. Soc.* 1997, 119, 4080), conjugate addition of  
16 diethylzinc to cyclic enones (F. Y. Zhang, A.S.C. Chan *Tetrahedron:  
17 Asymmetry* 1998, 9, 1179), and ring opening of epoxides (T. Iida et al.  
18 *Angew. Chem. Int. Ed. Engl.* 1998, 37, 2223). Incorporation of bromines  
19 into the 6 and 6' positions of BINOL, rather remote from the catalytic site,  
20 was shown to increase the enantioselectivity of the corresponding  
21 titanium catalysts in glyoxal-ene reactions (M. Terada et al.  
22 *Tetrahedron Lett.* 1994, 35, 1994). Bulky triarylsilyl groups at the 3 and 3'  
23 positions of BINOL led to increased levels of enantiofacial discrimination  
24 of prochiral aldehydes in asymmetric Diels-Alder reactions (Pu; *L. Chem.  
25 Rev.* 1998, 98, 2405). 3,3'-dinitrooctahydrobinaphthol was applied in  
26 titanium-catalyzed asymmetric oxidation of methyl-p-tolyl sulfide (Reetz,  
27 M. T. et al. *Tetrahedron Lett.* 1997, 38, 5273).

28

## 29 SUMMARY OF THE INVENTION

30 The present invention relates to new asymmetric aromatic ligands  
31 that may be used as catalysts. The ligand may be any aromatic ring system

1 containing one or more electronegative substituents. Preferably, the  
2 electronegative substituents are fluorine and the aromatic ring system is  
3 axially chiral, such as a biphenyl, binaphthyl or bipyridine derivative. In  
4 one preferred embodiment, the aromatic ring system is a binaphthyl  
5 derivative.

6 Fluorine substitution of aromatic groups modifies their properties  
7 including configurational stability and catalytic activity. One issue is the  
8 nature of steric and electronic effects of fluorination on aromatic based  
9 catalysts. The basic premise is that alteration of stabilizing stacking and  
10 edge-face interactions significantly affects approach of certain substrates to  
11 catalytic reaction centers. Due to fluorine's high electronegativity, electron  
12 density in fluoronaphthyl rings is located at the periphery, rather than  
13 in the ring's centre. The present invention will be illustrated by examples  
14 such as preparation of enantiomerically pure fluorobinaphthyl ligands  
15 and their application in catalytic asymmetric processes.

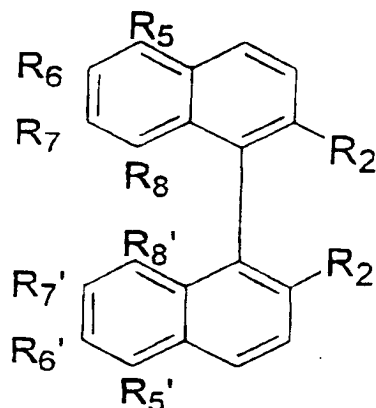
16 In one aspect of the present invention, there is provided an  
17 asymmetric ligand comprising an aromatic ring system substituted with  
18 at least one electronegative radical.

19 In another aspect, there is provided a method of producing a  
20 fluorinated asymmetric ligand having an aromatic ring system  
21 comprising fluorinating the aromatic ring system.

22 In yet another aspect, the present invention relates to asymmetric  
23 ligands comprising an aromatic ring system substituted with at least one  
24 electronegative substituent that is modified through nucleophilic  
25 substitution. Preferably, the electronegative substituent is fluorine, and  
26 the modification consists of displacing fluorine atoms on a  
27 polyfluorinated aromatic ring system with a nucleophile. As one  
28 example, the fluorine atoms at the 7 and 7' positions of 5,5',6,6',7,7',8,8'-  
29 octafluoro-2,2'-dihydroxy-1-1'-binaphthyl ( $F_8$ BINOL) are selectively  
30 displaced with a nucleophile.

Accordingly, the present invention also provides a compound having the Formula III:

Formula III



wherein R2 and R2' are the same or different and are OR where R may be hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR'R'' where R' and R'' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR'''R'''' where R''' and R'''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR''''R''''' where R'''' and R''''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; and R5, R5', R6, R6', R7, R7', R8 and R8' are independently hydrogen, fluorine, CN, NO<sub>2</sub>, OR (where R is as defined above), SO<sub>2</sub>Ar where Ar is any aromatic ring system, SPh, Cl, Br, I, N<sub>3</sub>, NR<sub>3</sub><sup>+</sup> where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH<sub>2</sub>, a

1 nucleophile X, wherein X may be OR<sub>9</sub>, NR<sub>10</sub>R<sub>11</sub>, SR<sub>12</sub>, SiR<sub>13</sub>R<sub>14</sub>R<sub>15</sub>,  
2 SeR<sub>16</sub> and wherein each of R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub> and R<sub>16</sub> may  
3 be the same or different and may be hydrogen, C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic,  
4 linear or branched, saturated or unsaturated, unsubstituted or substituted  
5 with N, O, S, or P; with the proviso that at least one of R<sub>5</sub> and R<sub>5'</sub>, R<sub>6</sub> and  
6 R<sub>6'</sub>, R<sub>7</sub> and R<sub>7'</sub>, and R<sub>8</sub> and R<sub>8'</sub> is electronegative.

7 In one preferred embodiment, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are the same and  
8 are H or F, and R<sub>5'</sub>, R<sub>6'</sub>, R<sub>7'</sub> and R<sub>8'</sub> are the same and are H or F, with the  
9 proviso that R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are not the same as R<sub>5'</sub>, R<sub>6'</sub>, R<sub>7'</sub> and R<sub>8'</sub>.

10 In another embodiment, R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>7</sub>, R<sub>7'</sub>, R<sub>8</sub> and R<sub>8'</sub> are all  
11 the same and are F.

12 More preferably, each of R, R', R'', R''', R'''', R''''', and R'''''' are H, or  
13 C<sub>1</sub>-C<sub>6</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated,  
14 unsubstituted or substituted with N, O, S or P; R<sub>7</sub> and R<sub>7'</sub> are the same  
15 and are a nucleophile X, and R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>8</sub> and R<sub>8'</sub> are the same and  
16 are F.

17 In still another aspect of the present invention, there is provided a  
18 method of generating a library of a predetermined number of asymmetric  
19 ligands comprising:

- 20 a) Providing an aromatic ring system having at least one  
21 electronegative substituent;
- 22 b) Selective substituting at least one electronegative substituent with  
23 a nucleophile; and
- 24 c) Repeating steps a) and b) a predetermined number of times to  
25 obtain a predetermined number of ligands.

26

27 Other features and advantages of the present invention will become  
28 apparent from the following detailed description. It should be  
29 understood, however, that the detailed description and the specific  
30 examples while indicating preferred embodiments of the invention are  
31 given by way of illustration only, since various changes and

1 modifications within the spirit and scope of the invention will become  
2 apparent to those skilled in the art from this detailed description.

3

#### 4 **BRIEF DESCRIPTION OF THE DRAWINGS**

5 The present invention will be better understood when the following  
6 description is read in connection with the accompanying drawings, in  
7 which:

8 Figure 1 shows the preparation of a modified polyfluorinated  
9 catalyst;

10 Figure 2 shows the configurational integrity of the  
11 polyfluorobinaphthyl core during nucleophilic modification;

12 Figure 3 is a schematic diagram showing the chemistry at the 7  
13 and 7' positions of the modified catalyst;

14 Figure 4 shows the attachment of a modified catalyst to an  
15 electrode surface;

16 Figure 5 shows experimentally observed cyclic voltammogram for  
17 the modified electrode surface;

18 Figure 6 shows the attachment of a modified catalyst to a solid  
19 surface;

20 Figure 7 shows the nucleophilic substitution at the 6, 6' positions  
21 of the modified catalyst;

22 Figure 8 is a schematic showing the chemistry of the nucleophilic  
23 modification at the 6 and 6' positions;

24 Figure 9 illustrates internal nucleophilic displacement in  
25 monoprotected F8BINOL; and

26 Figure 10 illustrates a synthesis scheme for preparing  $H_4F_4$  ligands.

27

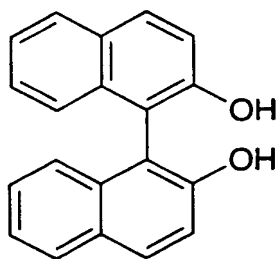
#### 28 **DESCRIPTION OF THE PREFERRED EMBODIMENT**

29 As previously mentioned, the present invention relates to aromatic  
30 asymmetric ligands containing at least one electronegative substituent.  
31 Optionally, the ligands may be modified with a nucleophile.

1       The present invention will be exemplified, by way of example by  
2 disclosing the design a new family of polyfluoroaryl ligands that originate  
3 from 2,2'-dihydroxy-1,1'-binaphthyl ("BINOL"), a catalyst precursor of  
4 broad utility in asymmetric catalysis (R. Noyori *Asymmetric Catalysis in*  
5 *Organic Synthesis*, Wiley: New York, 1994). The structure of BINOL is  
6 shown in Formula I:

7

8       Formula I



9

10

11       While the present invention will be described herein in relation to  
12 BINOL derivatives, it will be readily appreciated by those skilled in the art  
13 that other compounds having similar structures and properties may be  
14 substituted for BINOL. In particular, any aromatic ring structure is  
15 suitable for use in connection with the invention. For example, benzene,  
16 pyridine, naphthalene, anthracene and their derivatives are suitable for  
17 use with the invention (e.g. polyfluorinated benzene and polyfluorinated  
18 naphthalene). More preferably, the aromatic ring is one that exhibits axial  
19 chirality due to steric hinderance, i.e. the rings are not free to rotate about  
20 an axis because of steric hinderance. Such ring systems are known to  
21 those skilled in the art, and include biphenyl, binaphthyl, bipyridine and  
22 their derivatives.

23       More preferably, the aromatic ring structure is binaphthyl or a  
24 derivative thereof. Most preferably, the aromatic ring structure is a 2, 2'  
25 di-substituted binaphthyl derivative, where the substituent is hydroxy, C<sub>1</sub>-  
26 C<sub>6</sub> alkoxy, phenoxy, phosphino, phosphine oxide, primary or secondary

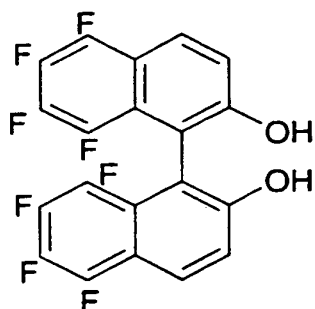
1 C<sub>1</sub>-C<sub>6</sub> amine, or primary or secondary sulfides. Some specific examples of  
2 such ring structures include the 2, 2' dihydroxy, 2, 2' dimethoxy, 2, 2'  
3 diphosphine, 2, 2' diphosphine oxide, and 2, 2' diamino derivatives of  
4 binaphthyl. Further, while it may be desirable, it is not necessary that the  
5 substituents at the 2 and 2' positions be the same. For example, the  
6 aromatic ring may be a 2-hydroxy, 2'-amino derivative or the like.

7 Furthermore, while the present invention is described generally in  
8 relation to being an aromatic ring substituted with fluorine, it will be  
9 appreciated that any relatively small electronegative radical may be  
10 utilized. Electronegative radicals are well known to those skilled in the  
11 art and include radicals such as CN and NO<sub>2</sub>, OR where R is as defined  
12 above, SO<sub>2</sub>Ar where Ar is any aromatic ring system, SPh, Cl, Br, I, N<sub>3</sub>,  
13 NR<sub>3</sub><sup>+</sup> where each R is the same or different and may be as defined above,  
14 OAr where Ar is as defined above, SR where R is as defined above, and  
15 NH<sub>2</sub>, that may be utilized in accordance with the present invention.  
16 Preferable electronegative substituents include F, Cl, Br, I, CN, and NO<sub>2</sub>.  
17 Fluorine is particularly useful in accordance with the present invention,  
18 since it is highly electronegative, and does not significantly affect the  
19 torsion angle of the aromatic moiety.

20 Without being limited by theory, the inventors postulate that since  
21 the van der Waals radius of fluorine atoms is about 0.27Å larger than that  
22 of hydrogen atoms (B.E. Smart *Organofluorine Compounds: Principles*  
23 *and Commercial Applications*, R.E. Banks, ed., Chapter 3, Plenum Press:  
24 New York, 1994), the replacement of hydrogens for fluorines at the 5, 5', 6,  
25 6', 7, 7', 8, and 8' positions of BINOL may affect the torsion angle  
26 minimally in the resulting 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-  
27 binaphthyl ("F<sub>8</sub>BINOL", Formula II below). More importantly,  
28 considerable electronic perturbations take place due to the net effect of  
29 eight fluorine atoms. The electron-deficient nature of the aromatic rings  
30 in Formula II should result in a higher oxidative stability compared to  
31 Formula I and increased acidity of the hydroxyl groups which could

1 potentially affect binding to metals and the corresponding substrates in  
2 the F<sub>8</sub>BINOL-mediated reactions. The increased acidity of the hydroxyl  
3 could also result in an increase in the lewis acidity of the bound metal  
4 compared to a non fluorinated binol analogue.

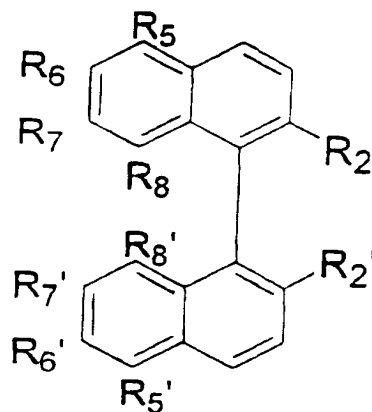
5  
6 Formula II



7  
8  
9  
10 Optionally, one or more of the electronegative radicals may be  
11 selectively substituted with a nucleophile. More preferably, one or more  
12 fluorine atoms on the aromatic ring system are selectively displaced with  
13 a nucleophile on a polyfluorinated catalyst such as the catalyst  
14 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F<sub>8</sub>BINOL).  
15 Ligands suitable for use as nucleophiles are well known to those skilled  
16 in the art and generally include radicals such as alcohols, amines, thiols  
17 and phenols. Some examples of suitable nucleophiles include NH<sub>2</sub><sup>-</sup>,  
18 PH<sub>3</sub>C<sup>-</sup>, PhNH<sup>-</sup>, ArS<sup>-</sup>, RO<sup>-</sup>, R<sub>2</sub>NH, ArO<sup>-</sup>, OH<sup>-</sup>, ArNH<sub>2</sub>, NH<sub>3</sub>, halogen, where,  
19 in each case, Ar is aromatic, and R may be the same or different and is C<sub>1</sub>-  
20 C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated,  
21 unsubstituted or substituted with N, O, S, or P.

The present invention also relates to compounds of the Formula III:

Formula III



wherein R2 and R2' are the same or different and are OR where R may be hydrogen, C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR'R'' where R' and R'' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR'''R'''' where R''' and R'''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR''''R''''' where R'''' and R''''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; and R5, R5', R6, R6', R7, R7', R8 and R8' are independently hydrogen, fluorine, CN, NO<sub>2</sub>, OR (where R is as defined above), SO<sub>2</sub>Ar where Ar is any aromatic ring system, SPh, Cl, Br, I, N<sub>3</sub>, NR<sub>3</sub><sup>+</sup> where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH<sub>2</sub>, a

1 each R is the same or different and may be as defined above, OAr where  
2 Ar is as defined above, SR where R is as defined above, NH<sub>2</sub>, a  
3 nucleophile X, wherein X may be OR<sub>9</sub>, NR<sub>10</sub>R<sub>11</sub>, SR<sub>12</sub>, SiR<sub>13</sub>R<sub>14</sub>R<sub>15</sub>,  
4 SeR<sub>16</sub> wherein each of R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, and R<sub>16</sub> may be  
5 the same or different and may be hydrogen, C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic,  
6 linear or branched, saturated or unsaturated, unsubstituted or substituted  
7 with N, O, S, or P; with the proviso that at least one of R<sub>5</sub> and R<sub>5'</sub>, R<sub>6</sub>  
8 and R<sub>6'</sub>, R<sub>7</sub> and R<sub>7'</sub>, and R<sub>8</sub> and R<sub>8'</sub> is electronegative.

9 In one preferred embodiment, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are the same and  
10 are H or F, and R<sub>5'</sub>, R<sub>6'</sub>, R<sub>7'</sub> and R<sub>8'</sub> are the same and are H or F, with the  
11 proviso that R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are not the same as R<sub>5'</sub>, R<sub>6'</sub>, R<sub>7'</sub> and R<sub>8'</sub>.

12 In another embodiment, R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>7</sub>, R<sub>7'</sub>, R<sub>8</sub> and R<sub>8'</sub> are all  
13 the same and are F.

14 In a preferred embodiment, R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>8</sub> and R<sub>8'</sub> are  
15 fluorine atoms; R<sub>7</sub> and R<sub>7'</sub> are the same, and are a nucleophile X. In  
16 another preferred embodiment, R<sub>5</sub>, R<sub>5'</sub>, R<sub>8</sub> and R<sub>8'</sub> are fluorine atoms,  
17 R<sub>6</sub> and R<sub>6'</sub> are the same and are a nucleophile X, and R<sub>7</sub> and R<sub>7'</sub> are the  
18 same and are a nucleophile Y where Y has the same definition as X and  
19 where X and Y may be the same or different.

20 Preferably, the nucleophiles X and Y are an OR group, where R is as  
21 defined above, and the modified catalyst is prepared from the bis  
22 (methylether) or bis(benzyl ether) of F<sub>8</sub>BINOL (i.e. where R<sub>2</sub> and R<sub>2'</sub> are  
23 methoxy, or benzyloxy) according to the reaction scheme shown in Figure  
24 1.

25 More preferably, the nucleophiles X and Y are a methoxy or ethoxy  
26 group. It will be understood by those skilled in the art that different  
27 catalytic applications will have different preferred substituents.

28 While the foregoing describes nucleophilic substitution of  
29 F<sub>8</sub>BINOL at the 7 and 7' positions, it will be readily appreciated by those  
30 skilled in the art that the fluorine atoms at other positions may be  
31 additionally or alternately substituted. For example, Figure 7 shows the

1 selective displacement of fluorine atoms at positions 6 and 6' with the  
2 nucleophiles X and Y in a modified F<sub>8</sub>BINOL containing the ligand A, B  
3 or C (where A, B, and C may independently be as previously defined for  
4 X) groups at positions 7 and 7'. Figure 8 shows the stereochemistry of a  
5 modified F<sub>8</sub>BINOL containing nucleophiles at the 6, 6', 7 and 7' positions.  
6 In this manner, a matrix of different catalysts may be prepared. Such a  
7 matrix is useful in determining what combination of substitutions is  
8 most useful for any particular catalytic application.

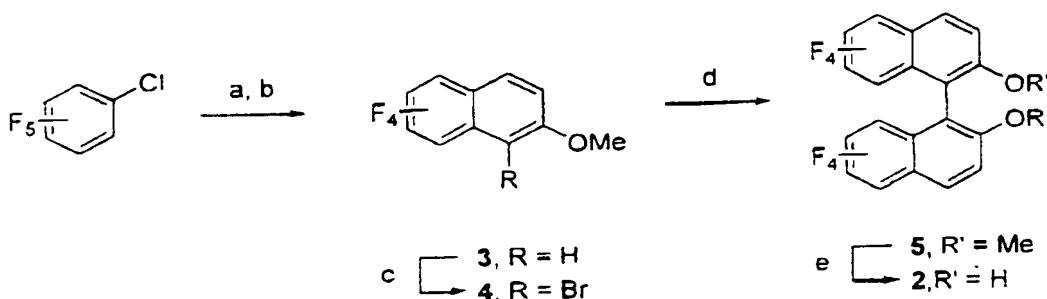
9 Selective substitution of the fluorine groups at the 7 and 7'  
10 positions with the methoxy group takes place in 95% yield with  
11 remarkable selectivity. The configuration integrity of the  
12 polyfluorobinaphthyl core during the methoxylation process is shown in  
13 Figure 2.

14 Figure 3 is a schematic diagram showing the chemistry of the  
15 modified catalyst at the 7 and 7' positions. The favourable conformation  
16 of the modified catalyst leads to many improved properties and utilities  
17 for the catalyst. For example, facile modification at the 7,7' positions  
18 suggests the possibility of placing the catalytic reaction center in that area.  
19 Direct connection of heteroatoms by nucleophilic substitution should  
20 lead to novel C<sub>2</sub> symmetrical ligands. Their monodentate nature will  
21 result from the steric constraints that should defeat chelation. In order to  
22 create different bidentate sites at the 7 and 7' positions, linkers of varied  
23 lengths may be attached to the 7 and 7' positions. Examples of linkers and  
24 their methods of attachment are well known in the art. Examples of  
25 linkers include -OCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, -OCH<sub>2</sub>CH<sub>2</sub>OH, -OCH<sub>2</sub>NH<sub>2</sub>, -OCH<sub>2</sub>PH<sub>2</sub>, -  
26 CH<sub>2</sub>CH<sub>2</sub>SH, etc.

27 It will be appreciated by those skilled in the art that the compounds  
28 of the present invention may be in racemic or optically pure form. In a  
29 preferred embodiment, the compounds are in the optically pure S form.

30 The examples following particularize the preparation of  
31 compounds within the scope of the present invention. Generally

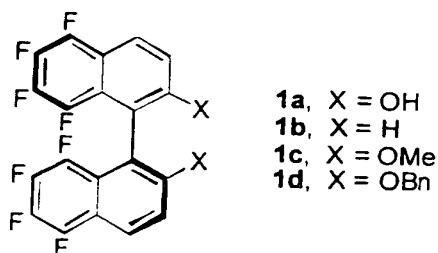
speaking, unsubstituted polyfluorinated compounds may be prepared according to Scheme 1. While reference is made to fluorinated aromatics, it will be appreciated that similar standard processes may be used for other compounds within the scope of the present invention.

Scheme 1<sup>a</sup>

<sup>a</sup>Key: (a) *n*-BuLi, ether, -78 °C; (b) 3-methoxythiophene, -78 °C to r.t.; (c) NBS, acetonitrile, r.t.; (d) Cu<sup>0</sup>, 175 °C; (e) BBr<sub>3</sub>, dichloromethane, r.t.

Nucleophilic displacement of aromatic fluorine is a well known reaction with a wide scope and utility [Welch, 2000 #14]. The presence of the fluorine atoms in the 2,2' dihydroxy BINOL derivative (compound 1a in Formula IV) suggests nucleophilic substitution as a potential route to ligand modification. Standard methoxylation with NaOMe of 5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl (compound 1b in Formula IV) results in nucleophilic substitution of fluorine, but a complicated mixture of poly(methoxylated) products is obtained, indicating lack of regioselectivity. However, the presence of the methoxy substituents at the 2 and 2' positions in the bis(methyl) ether (compound 1c in Formula IV) is sufficient to secure high regioselectivity of the methoxylation reaction. Double substitution proceeds smoothly and results in the 7,7'-bis(methoxy) product in good chemical yield and with high regioselectivity.

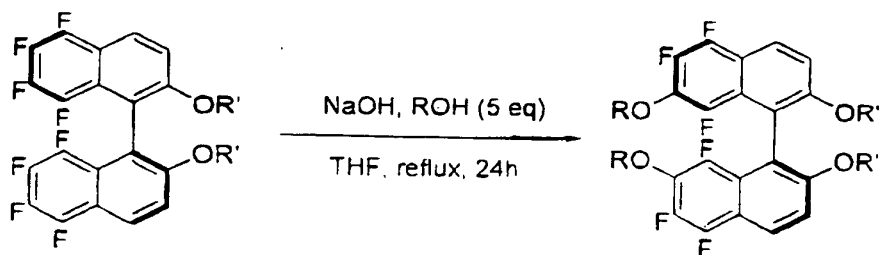
## Formula IV



Other alkoxy nucleophiles behave in a similar manner and may be similarly substituted (See Scheme 2 below). However, subsequent dealkylation with boron tribromide suffers from poor chemoselectivity. Therefore, the use of the bis(benzyl) ether (compound 1d in Formula IV) or another selective protective group which benefits from selective deprotection via hydrogenation, is preferable in order to arrive at the final bis-2,2'-hydroxy stage.

No racemization is observed when enantiomerically pure bis(methoxy) derivative (compound 1c in Formula IV) is used in the methoxylation reaction.

## Scheme 2



R	R'	yield (%)
Me	Me	95
Et	Bn	88
<i>i</i> Pr	Bn	88
<i>t</i> Bu	Bn	88

1        It will, of course, be appreciated that the nucleophilical substitution  
2 process may be utilized with not only the binaphthyl derivatives above  
3 described, but with any of the aromatic ring systems previously described.  
4 For example, the selective substitution may be used on polyfluorinated  
5 benzene or polyfluorinated naphthalene systems, or indeed any aromatic  
6 ring system having at least one electronegative radical.

7        Those skilled in the art will understand that the compounds of the  
8 present invention have many useful applications. Such applications  
9 include asymmetric catalysis with main group elements, transition metal  
10 and lanthanide metals; asymmetric reagent with main group elements,  
11 transition metal and lanthanide metals; polymer supported catalysis;  
12 incorporation of molecules into crown ethers for development of phase  
13 transfer catalysts; use of compounds as a monomer for polymerization;  
14 asymmetric polymer supported electrochemical oxidation catalysis; as a  
15 chiral auxiliary in an asymmetric reaction; as a resolving agent for chiral  
16 compounds, including but not limited to amines; asymmetric catalysis  
17 (reagent) in fluorine phase reactions; as a chiral stationary phase for  
18 HPLC and other chromatographic techniques; phase transfer catalyst  
19 between organic, fluorine phase and alkali solutions.

20        One specific application is to develop combinatorial approaches to  
21 catalyst development. It is possible to determine which substitution  
22 pattern on the  $F_8$ BINOL moiety gives optimal catalyst with regard to rate  
23 and selectivity in a particular reaction. To address this issue, the dihedral  
24 angle and electron distribution in  $F_8$ BINOL may be varied by replacing  
25 fluorine atoms at the 7,7' positions with a variety of nucleophiles to  
26 develop analogs of  $F_8$ BINOL.

27        It is also possible to generate libraries of such analogs using  
28 solution and solid-phase parallel synthesis. The structure/activity  
29 relationships may be deciphered based on screening the resulting catalyst  
30 libraries in a variety of reactions including hetero Diels-Alder,  
31 aziridination, direct aldol, and imine hydrogenation processes.

1       A library of compounds may also be generated for any other  
2       suitable purpose. For example, it is possible to build a library of  
3       compounds for pharmaceutical testing. With the highly selective  
4       substitution, it is possible to start with a base compound and develop a  
5       number of related but different compounds by selectively substituting  
6       different nucleophiles at the same or different locations on the base  
7       compound. Pharmacological activity screening may then be done on the  
8       library of compounds to determine which compounds have the highest  
9       activity.

10       The highly selective nucleophilic functionalization of the  $F_8$ BINOL  
11       core will allow the attachment of the modified catalysts to an electrode  
12       surface or a solid support. Figure 4 shows the attachment of the modified  
13       catalyst to an electrode surface and Figure 5 shows experimentally  
14       observed cyclic voltammogram for the modified electrode surface.

15       Figure 6 shows the attachment of the modified catalyst to a solid  
16       support. In particular, Figure 6 exemplifies an approach toward libraries  
17       of TentaGel S OH resin-linked catalysts. An alternative to this strategy is  
18       to introduce functionality X directly onto the ligand-derivatized resin. On  
19       bead screening for the catalytic activity will allow the fine-tuning of the  
20       ligand's torsion angle using solid-phase chemistry by manipulating the  
21       7,7' substituents. It should be emphasized that established routes to  
22       modified BINOL involve rather harsh electrophilic functionalization  
23       which puts substituents into the 6,6' positions and necessitates a  
24       subsequent resolution step which is not feasible under combinatorial  
25       protocols commonly performed on a microgram scale. On the contrary,  
26       high configurational stability of  $F_8$ BINOL under basic conditions will  
27       enable the use the homochiral starting material without the loss of  
28       enantiomeric purity during the nucleophilic substitution. As well,  
29       substituents at the 7,7' positions could have direct steric influence over  
30       the dihedral angle which should modulate the catalytic activity, a feature  
31       not available for the 6,6' substitution pattern.

Figure 9 shows internal nucleophilic displacement in monoprotected F<sub>8</sub>BINOL which illustrates that the axial chirality of F<sub>8</sub>BINOL provides convenient access to ligands with helical chirality.

Utility of the poly(alkoxylated) ligands in asymmetric catalysis was illustrated using diethylzinc addition to aldehydes. We observed high levels of enantioselectivity in titanium-catalyzed addition of diethylzinc to aldehydes using x and x under the conditions where the formation of the monomeric catalysts of 1:1 composition is favored.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

The following examples, which are non-limiting, are illustrative of the present invention. The scope of the invention is limited only by the claims.

## EXAMPLES

### I. FLUORINE SUBSTITUTION OF BINOL

#### (a) 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl

Racemic form of the compound 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (compound 2 in Scheme 1) was prepared according to Scheme 1 above. Tetrafluorobenzene, formed by treating commercially available chloropentafluorobenzene with *n*-butyllithium at -78°C, was reacted with 3-methoxythiophene, obtained from 3-bromothiophene using a literature procedure (methoxythiophene preparation). Upon the *in situ* extrusion of sulfur, 2-methoxy-5,6,7,8-tetrafluoronaphthalene (Formula III) was obtained in 52% yield. 5,6,7,8-Tetrafluoro-2-naphthol, prepared from 2-methoxy-5,6,7,8-tetrafluoronaphthalene by demethylation with BBr<sub>3</sub>, did not undergo the FeCl<sub>3</sub>-catalyzed oxidative coupling, commonly used for the preparation of BINOL from 2-naphthol (BINOL prep via FeCl<sub>3</sub> coupling). Instead,

1 substitution of hydrogen for chlorine at the 1 position of the aromatic  
2 ring took place. Higher oxidation potential of 5,6,7,8-tetrafluoro-2-  
3 naphthol (2.07V *vs* Ag/AgCl compared to 1.47V *vs* Ag/AgCl for BINOL)  
4 is a likely reason for the lack of reactivity in the oxidative coupling.

5 Therefore, the reductive route through intermediacy of the 1-  
6 brominated derivative (compound 4 in Scheme 1), prepared in 52% yield  
7 from compound 3 in Scheme 1 by treatment with *N*-bromosuccinimide  
8 in acetonitrile, was utilized. The Ullmann homocoupling of the 1-bromo  
9 derivative, facilitated by the presence of aromatic fluorines, gave the  
10 desired bis(methoxy) product (compound 5 in Scheme 1) in 85% yield.  
11 Demethylation of the bis(methoxy) derivative with  $\text{BBr}_3$  furnished  
12  $\text{F}_8\text{BINOL}$  (compound 2 in Scheme 1) in 88% yield. Finally,  
13 recrystallization from methanol/water gave pure  $\text{F}_8\text{BINOL}$  as white  
14 needles. After several unsuccessful attempts at resolving  $\text{F}_8\text{BINOL}$ , the  
15 diastereomeric bis(menthyl)carbonates were chromatographically  
16 separated by reacting racemic  $\text{F}_8\text{BINOL}$  with excess (-)-  
17 menthylchloroformate. Treatment of each diastereomer with dilute  
18 NaOH followed by extraction with diethyl ether afforded (-)- $\text{F}_8\text{BINOL}$  and  
19 (+)- $\text{F}_8\text{BINOL}$ , respectively. The enantiomeric excess, determined using  
20 chiral HPLC (Chiralpak AD column), was found to be >99.9% in each case.  
21

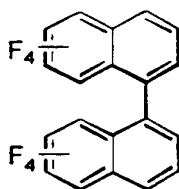
#### 22 (b) 5,6,7,8-tetrafluoro-1-naphthol

23 Replacement of aromatic hydrogens for fluorines is known to  
24 substantially increase barriers to axial torsion in substituted biphenyls. For  
25 example, fluorination of the 4 and 5 positions of 9,10-  
26 dihydrophenanthrene raises the torsion barrier from 4.1 to 10.3 kcal/mol  
27 (M. Schlosser, D. Michel *Tetrahedron* 1996, 52, 99 and references cited  
28 therein). In order to estimate the effect of polyfluorination on  
29 atropisomerism in the octafluoro-1,1'-binaphthyl species racemic 5,6,7,8-  
30 octafluoro-1,1'-binaphthyl (compound 6 below) was prepared and its X-ray  
31 structure determined. Racemic 5,6,7,8-octafluoro-1,1'-binaphthyl was

1 prepared from 5,6,7,8-tetrafluoro-1-naphthol (G. W. Gribble, C. G.  
2 LeHoullier, M. P. Sibi, R. W. Allen *J. Org. Chem.* 1985, 50, 1611) by Ni(0)-  
3 catalyzed homocoupling of its trifluoromethanesulfonate ester in NMP at  
4 100 °C. The torsion angles in the molecular structures of BINOL and  
5 F<sub>8</sub>BINOL were not compared due to the possibility of intramolecular OH-  
6 F hydrogen bonding in the crystal lattice that could have complicated  
7 direct comparison of geometric parameters. Remarkably, the torsion angle  
8 between the two tetrafluorinated naphthyl planes in 5,6,7,8-octafluoro-  
9 1,1'-binaphthyl is only 0.7° larger than in the parent hydrido derivative  
10 (70.2° for octafluoro-1,1'-binaphthyl *vs* 69.5° for 1,1'-binaphthyl (R.  
11 Kuroda, S. F. Martin *J. Chem. Soc. Perkin Trans II* 1981, 167)).

12 To further understand atropisomerism in F<sub>8</sub>BINOL acid-promoted  
13 racemization of its (-) enantiomer was investigated. This process is  
14 known to operate for BINOL. Remarkably, F<sub>8</sub>BINOL remains optically  
15 active (99.9% e.e) after 24 hours in boiling THF/HCl mixture, whereas  
16 BINOL rapidly racemizes under these conditions!

17



6

18

19

20

21 Polyfluorination of aromatic nuclei is also known to decrease pKa's  
22 of bound heteroatoms (B. E. Smart, in: *Organofluorine compounds:  
23 Principles and Commercial Applications* (R. E. Banks, ed.), Chapter 3,  
24 Plenum Press: New York, 1994). For example, incorporation of four  
25 fluorine atoms into the aromatic skeleton of tyrosine results in the pKa'  
26 decrease of the ring-bound hydroxyl group by 5 units (K. Kim, P. A. Cole *J.*

1 *Am. Chem. Soc.* 1998, 120, 6851). It was determined that the pKa' of the  
2 hydroxyl group in F<sub>8</sub>BINOL decreases by 1 unit upon octafluorination  
3 (BINOL: pKa' 10.28; F<sub>8</sub>BINOL: pKa' 9.29). Another important consequence  
4 of fluorination is anodic shift in the oxidation potential of F<sub>8</sub>BINOL,  
5 which was found to be more positive than that of binaphthyl by 0.6 V, a  
6 useful property for applications in oxidation catalysis.

7 These results lead to the conclusion that the effect of fluorine on the  
8 reactivity of F<sub>8</sub>BINOL is primarily electronic in nature. The desired  
9 conformational flexibility, one of the most important characteristics of  
10 BINOL allowing it to coordinate a wide variety of metals, should be  
11 preserved. Remarkable configurational stability of either enantiomer of  
12 F<sub>8</sub>BINOL is perhaps its most valuable property.

13

## 14 II. NUCLEOPHILIC SUBSTITUTION

15

16 General: Anhydrous THF was obtained by distillation over sodium  
17 benzophenone ketyl under nitrogen. 2,2'-dimethoxy-5,5',6,6',7,7',8,8'-  
18 octafluoro-1,1'-binaphthyl and 2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octafluoro-  
19 1,1'-binaphthyl were prepared according to literature procedures. Column  
20 chromatography was carried out using 230-400 mesh silica gel.

21

### 22 (a) 2,2',7,7'-tetramethoxy-5,5',6,6',8,8'-hexafluoro-1,1'-binaphthyl(1)

23 To a solution of 2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-  
24 binaphthyl (91.7mg, 0.2mmol) in anhydrous THF (10mL) was added 81μl  
25 (2.0mmol) methanol and 112mg (2.0mmol) KOH. The mixture was  
26 stirred and refluxed for 12hrs. The reaction mixture was diluted with  
27 ether and washed with aqueous HCl (5%). The result organic extract was  
28 dried over MgSO<sub>4</sub> and concentrated. Purification of the residue by  
29 chromatography over silica afforded pure (1) (91.0mg, 84%) as white solid.

1 <sup>1</sup>HNMR(400 MHz, CDCl<sub>3</sub>): δ 8.10(d, J=9.2Hz, 2H), 7.42(d, J=9.2Hz, 2H),  
2 3.91(s, 6H), 3.75(s, 6H). <sup>19</sup>FNMR(400MHz, CDCl<sub>3</sub>): δ -140.93(d, J=16.8Hz), -  
3 152.65(dd, J=16.8Hz, 3.2Hz), -158.80(d, J=19.6Hz). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>):  
4 δ 155.6(s), 147.2(dt, J=249.2Hz, 3.8Hz), 142.4(ddd, J=249.0Hz, 6.1Hz, 4.6Hz),  
5 139.9(ddd, J=250.0Hz, 9.2Hz, 4.5Hz), 135.9(m), 121.6(m), 120.9(m), 117.2(s),  
6 116.0(dd, J=9.9Hz, 4.5Hz), 114.3(s), 62.5(s), 56.9(s). HREI-MS, m/z: Calcd for  
7 C<sub>24</sub>H<sub>16</sub>F<sub>6</sub>O<sub>4</sub> 482.0953; found, 482.0958.

8

9 (b) 2,2'-dimethoxy-7,7'-diethoxy-5,5',6,6',8,8'-hexafluoro-1,1'-  
10 binaphthyl(2)

11 In accordance to the general procedure described above, but 116μl  
12 (2.0mmol) ethanol was used instead of methanol. A total of 78.1mg (77%)  
13 of 2 was obtained as white solid.

14 <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>): δ 8.09(d, J=9.2Hz, 2H), 7.38(d, J=9.6Hz, 2H),  
15 4.11(q, J=6.8Hz, 4H), 3.73(s, 6H), 1.29(t, J= 6.8Hz, 6H). <sup>19</sup>FNMR(400MHz,  
16 CDCl<sub>3</sub>): δ -139.91(d, J=16.8Hz), -152.68(dd, J=16.8Hz, 2.8Hz), -158.08(d,  
17 J=19.6Hz). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>): δ 155.6(s), 147.6(dt, J=249.3Hz, 3.8Hz),  
18 142.3(ddd, J=247.0Hz, 6.0Hz, 4.6Hz), 140.2(ddd, J=246.0Hz, 9.2Hz, 4.5Hz),  
19 134.8(m), 121.5(m), 120.9(m), 117.2(s), 116.1(dd, J=9.8Hz, 3.8Hz), 114.2(s),  
20 71.0(s), 56.9(s), 15.5(s). HREI-MS, m/z: Calcd for C<sub>26</sub>H<sub>20</sub>F<sub>6</sub>O<sub>4</sub>, 510.1255;  
21 found, 510.1266.

22

23 (c) 2,2'-dimethoxy-7,7'-di-*iso*-propoxy-5,5',6,6',8,8'-hexafluoro-1,1'-  
24 binaphthyl(3)

25 In accordance to the general procedure described above, but 154μl  
26 (2.0mmol) *iso*-propanol was used instead of methanol. A total of 87.9mg  
27 (89%) of 3 was obtained as white foam.

28 <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>): δ 8.08(d, J=9.2Hz, 2H), 7.38(d, J=9.2Hz, 2H),  
29 4.36(sep, J=6.0Hz, 2H), 3.71(s, 6H), 1.23(dd, J=6.0Hz, 3.2Hz, 12H).

1 <sup>19</sup>FNMR(400MHz, CDCl<sub>3</sub>): δ -157.19(d, J=19.6Hz), -152.81(dd, J=16.8Hz,  
2 2.8Hz), -138.60(d, J=16.8Hz). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>): δ 155.6(s), 148.2(dt,  
3 J=250.0Hz, 3.8Hz), 142.3(ddd, J=247.0Hz, 6.0Hz, 4.6Hz), 140.6(ddd,  
4 J=245.0Hz, 9.2Hz, 3.8Hz), 133.8(m), 121.5(m), 120.9(m), 117.3(s), 116.2(dd,  
5 J=10.6Hz, 3.8Hz), 114.2(s), 77.7(s), 56.8(s), 22.4(s). HREI-MS m/z: Calcd for  
6 C<sub>28</sub>H<sub>24</sub>F<sub>6</sub>O<sub>4</sub> 538.1583; found, 538.1579.

7  
8 (d) 2,2'-dimethoxy-7,7'-dibenzoyloxy-5,5',6,6',8,8'-hexafluoro-1,1'-  
9 binaphthyl(4)

10 In accordance to the general procedure described above, but 207μl  
11 (2.0mmol) benzyl alcohol was used instead of methanol. A total of  
12 98.6mg(78%) of 4 was obtained as white foam. <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>):  
13 δ8.07(d, J=9.2Hz, 2H), 7.37-7.22(m, 12H), 5.06(s, 4H), 3.68(s, 6H).  
14 <sup>19</sup>FNMR(400MHz, CDCl<sub>3</sub>): δ -138.78(d, J=16.8Hz), -152.49(dd, J=16.8Hz,  
15 2.8Hz), -157.48(d, J=20.8Hz). <sup>13</sup>CNMR(100MHz, CDCl<sub>3</sub>): δ155.6(s), 147.6(dt,  
16 J=250.0Hz, 3.8Hz), 142.3(ddd, J=247.0Hz, 6.8Hz, 4.6Hz), 140.1(ddd,  
17 J=246.0Hz, 9.1Hz, 3.8Hz), 136.3(s), 134.4(m), 128.7(d, J=3.1Hz), 128.6(d,  
18 J=4.6Hz), 128.5(s), 121.6(m), 120.9(m), 117.2(s), 116.2(dd, J=9.8Hz, 4.6Hz),  
19 114.3(s), 76.5(s), 56.9(s). HREI-MS, m/z: Calcd for C<sub>36</sub>H<sub>24</sub>F<sub>6</sub>O<sub>4</sub>, 634.1560;  
20 found, 634.1579.

21

22 (e) 2,2'-dibenzoyloxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl(5)

23 To a solution of 2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-  
24 binaphthyl (215.2mg, 0.5mmol) and potassium carbonate (691mg, 5mmol)  
25 in THF(15mL) was added benzyl bromide (0.6mL, 5mmol). The mixture  
26 was stirred and refluxed for 20hrs. The reaction mixture was diluted with  
27 ether and washed with aqueous HCl (5%). The solvent and excess benzyl  
28 bromide were removed under reduced pressure. Recrystallization from a  
29 Hexanes and dichloromethane mixture gave white solid (224.2mg, 80%).

1 <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>): δ8.16(d, J=9.6Hz, 2H), 7.50(d, J=9.6Hz, 2H), 7.23-  
2 7.16(m, 6H), 6.98-6.96(m,4H), 5.12(s, 4H). <sup>19</sup>FNMR(300MHz, CDCl<sub>3</sub>): δ-  
3 146.72(t, J=17.7Hz), -150.55(dd, J=16.2Hz, 5.1Hz), -158.68(t, J=20.1Hz), -  
4 163.22(t, J=20.1Hz).

5  
6 (e) 2,2'-dibenzyloxy-7,7'-dimethoxy-5,5',6,6',8,8'-hexafluoro-1,1'-  
7 binaphthyl(6)

8 To a solution of 2,2'-dibenzyloxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-  
9 binaphthyl(5) (224.2mg, 0.4mmol) and potassium hydroxide (224mg,  
10 4.0mmol) in THF(20mL) was added methanol (162μl, 4.0mmol). The  
11 mixture was stirred and refluxed for 12hrs. The reaction mixture was  
12 diluted with ether and washed with aqueous HCl (5%). The result organic  
13 extract was dried over MgSO<sub>4</sub> and concentrated. Purification of the  
14 residue by chromatography over silica afforded pure (6) as white foam  
15 (197.9mg, 78%). <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>): δ7.93(d, J=9.2Hz, 2H), 7.24(d,  
16 J=9.6Hz, 2H), 7.01-6.96(m, 6H), 6.76(d, J=7.2Hz, 4H), 4.90(s, 4H), 3.74(s, 6H).  
17 <sup>19</sup>FNMR(300MHz, CDCl<sub>3</sub>): δ-140.18(d, J=17.3Hz), -152.35(dd, J=16.7Hz,  
18 3.1Hz), -158.30(d, J=21.5Hz).

19  
20 (f)2,2'-dihydroxy-7,7'-dimethoxy-5,5',6,6',8,8'-hexafluoro-1,1'-  
21 binaphthyl(7)

22 To a solution of 2,2'-dibenzyloxy-7,7'-dimethoxy-5,5',6,6',8,8'-  
23 hexafluoro-1,1'-binaphthyl(6) (126.5mg, 0.2mmol) was added  
24 Pd/C(85.2mg, 10%) under a hydrogen atmosphere at room temperature.  
25 After being stirred at the same temperature for 10hrs, the reaction  
26 mixture was filtered and concentrated. Purification of the residue by  
27 chromatography over silica afforded pure (7) (quantitatively) as white  
28 foam. <sup>1</sup>HNMR(400MHz, CDCl<sub>3</sub>): δ8.06(d, J=8.8Hz, 2H), 7.30(d, J=9.2Hz, 2H),  
29 5.39(s, 2H), 3.92(s, 6H). <sup>19</sup>FNMR(400MHz, CDCl<sub>3</sub>): δ -142.14(d, J=15.2Hz), -

- 24 -

1 151.24(dd, J=16.8Hz, 2.8Hz), -157.16(d, J=19.6Hz).  $^{13}\text{C}$ NMR(100MHz,  $\text{CDCl}_3$ ):  
2  $\delta$  153.2(s), 146.6(dt, J=248.5Hz, 3.8Hz), 142.7(ddd, J=248.0Hz, 6.0Hz, 4.6Hz),  
3 140.3(ddd, J=248.0Hz, 8.3Hz, 4.6Hz), 136.7(m), 123.5(m), 120.5(m), 118.5(s),  
4 115.9(dd, J=10.6Hz, 3.8Hz), 108.6(s), 62.5(m). HREI-MS: m/z: calcd for  
5  $\text{C}_{22}\text{H}_{12}\text{F}_6\text{O}_4$  454.0642; found, 454.0640.

6

7

8

## 1 WHAT IS CLAIMED IS:

2

3 1. An asymmetric ligand comprising an aromatic ring system substituted  
4 with at least one electronegative radical.

5

6 2. The ligand as claimed in claim 1 wherein the aromatic ring system  
7 comprises benzene, pyridine, naphthalene, anthracene or a derivative  
8 thereof.

9

10 3. The ligand as claimed in claim 1 wherein the aromatic ring system is  
11 axially chiral.

12

13 4. The ligand as claimed in claim 3 wherein the aromatic ring system  
14 comprises a biphenyl, binaphthyl, bipyridine ring system or a  
15 derivative thereof.

16

17 5. The ligand as claimed in claim 4 wherein the aromatic ring system  
18 comprises a binaphthyl derivative.

19

20 6. The ligand as claimed in claim 5 wherein the aromatic ring system  
21 comprises a 2, 2' di substituted binaphthyl ring system.

22

23 7. The ligand as claimed in claim 6 wherein the aromatic ring system is a  
24 2, 2' di substituted binaphthyl ring system, and wherein the  
25 substituents at the 2 and 2' positions are the same or different, and are  
26 each OR where R may be hydrogen, C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear  
27 or branched, saturated or unsaturated, unsubstituted or substituted  
28 with N, O, S, or P, PR'R'' where R' and R'' are the same or different  
29 and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or  
30 branched, saturated or unsaturated, unsubstituted or substituted with  
31 N, O, S, or P, phosphine oxide, NR'''R'''' where R''' and R'''' are the

1 same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic,  
2 aliphatic, linear or branched, saturated or unsaturated, unsubstituted  
3 or substituted with N, O, S, or P, SR<sup>''''</sup>R<sup>''''</sup> where R<sup>''''</sup> and R<sup>''''</sup> are  
4 the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be  
5 aromatic, aliphatic, linear or branched, saturated or unsaturated,  
6 unsubstituted or substituted with N, O, S, or P.

7

8 8. The ligand as claimed in claim 7 wherein R is hydrogen, or C<sub>1</sub>-C<sub>6</sub> alkyl  
9 which is linear or branched.

10

11 9. The ligand as claimed in any one of claims 1 to 8 wherein the  
12 electronegative radical is fluorine, Cl, Br, I, CN, or NO<sub>2</sub>.

13

14 10. The ligand as claimed in any one of claims 1 to 8 wherein the  
15 electronegative radical is fluorine.

16

17 11. The ligand as claimed in any one of claims 1 to 8 wherein the aromatic  
18 ring system is polyfluorinated.

19

20 12. The ligand as claimed in claim 6 or 7 wherein the 5, 6, 7, and 8  
21 positions of the binaphthyl ring system are fluorinated and the 5', 6',  
22 7', and 8' positions of the binaphthyl ring system are not substituted  
23 with an electronegative radical.

24

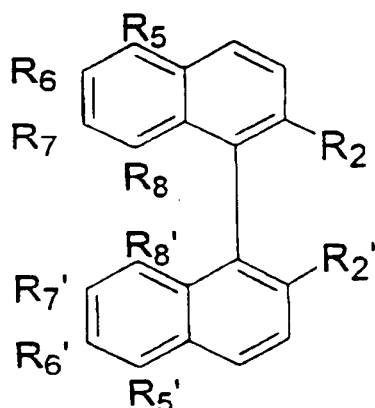
25 13. The ligand as claimed in claim 6 or 7 wherein the 5, 6, 7, and 8  
26 positions of the binaphthyl ring system are not substituted with an  
27 electronegative radical, and the 5', 6', 7', and 8' positions of the  
28 binaphthyl ring system are fluorinated.

29

14. The ligand as claimed in claim 5, 6, 7 or 8 wherein the electronegative radical is fluorine, and the binaphthyl ring system is fluorinated at the 5, 5', 6, 6', 7, 7', 8 and 8' positions.

15. The ligand as claimed in claim 8 which is selected from the group of ligands comprising 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dimethoxy-1,1'-binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-n-propoxy-1,1'-binaphthyl and 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-i-propoxy-1,1'-binaphthyl.

16. A compound of the formula III:



wherein R<sub>2</sub> and R<sub>2</sub>' are the same or different and are OR where R may be hydrogen, C<sub>1</sub>-C<sub>20</sub> alkyl aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR'R'' where R' and R'' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR'''R'''' where R''' and R'''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR''''R''''''

1 where R'''' and R''''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub>  
2 that may be aromatic, aliphatic, linear or branched, saturated or  
3 unsaturated, unsubstituted or substituted with N, O, S, or P; and  
4

5 R5, R5', R6, R6', R7, R7', R8 and R8' are independently hydrogen, fluorine,  
6 CN, or NO<sub>2</sub>, OR (where R is as defined above), SO<sub>2</sub>Ar where Ar is any  
7 aromatic ring system, SPh, Cl, Br, I, N<sub>3</sub>, NR<sub>3</sub><sup>+</sup> where each R is the same  
8 or different and may be as defined above, OAr where Ar is as defined  
9 above, SR where R is as defined above, NH<sub>2</sub>, a nucleophile X, wherein X  
10 may be OR<sub>9</sub>, NR<sub>10</sub>R<sub>11</sub>, SR<sub>12</sub>, SiR<sub>13</sub>R<sub>14</sub>R<sub>15</sub>, SeR<sub>16</sub> and wherein each of  
11 R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub> and R<sub>16</sub> is the same or different and may  
12 be hydrogen, C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched,  
13 saturated or unsaturated, unsubstituted or substituted with N, O, S, or P,  
14 with the proviso that at least one of R5, R5', R6, R6', R7, R7', R8 and R8' is  
15 electronegative.

16

17 17. The compound as claimed in claim 16 wherein R5, R6, R7 and R8 are  
18 the same and are H or F, and R5', R6', R7' and R8' are the same and are  
19 different than R5, R6, R7 and R8.

20

21 18. The compound as claimed in claim 16 wherein R2 and R2' are the  
22 same or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or  
23 branched, and R5, R5', R6, R6', R7, R7', R8 and R8' are each fluorine.

24

25 19. The compound as claimed in claim 16 wherein R2 and R2' are the  
26 same or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or  
27 branched, and R5, R5', R6, R6', R8 and R8' are each fluorine, and R7  
28 and R7' are the same or different and are a nucleophile X as claimed in  
29 claim 16.

30

- 1    20. The compound as claimed in claim 16 wherein R2 and R2' are the  
2       same or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or  
3       branched, and R5, R5', R8 and R8' are each fluorine, and R6, R6', R7,  
4       R7' are the same or different and are a nucleophile X as claimed in  
5       claim 13.  
6
- 7    21. The compound as claimed in claim 19 or 20 wherein the nucleophile  
8       X is hydroxy or C<sub>1</sub>-C<sub>6</sub> alkoxy.  
9
- 10   22. A modified polyfluorinated binaphthyl based ligand wherein the  
11       fluorine atoms in at least one of positions 5 and 5', 6 and 6', 7 and 7',  
12       and 8 and 8' is selectively displaced with a nucleophile.  
13
- 14   23. The modified polyfluorinated binaphthyl based ligand as claimed in  
15       claim 22 wherein the fluorine atoms at positions 7 and 7' are  
16       selectively displaced with a nucleophile.  
17
- 18   24. The modified polyfluorinated binaphthyl based ligand as claimed in  
19       claim 23 wherein the fluorine atoms at positions 6, 6', 7 and 7' are  
20       selectively displaced with a nucleophile.  
21
- 22   25. A ligand as claimed in any one of claims 1 to 24 wherein the ligand is  
23       linked to a solid support.  
24
- 25   26. A ligand as claimed in any one of claims 1 to 24 wherein the ligand is  
26       linked to an electrode surface.  
27
- 28   27. The use a ligand as claimed in any one of claims 1 to 26 for an  
29       application selected from the group consisting of asymmetric catalysis  
30       with main group elements, transition metal and lanthanide metals,  
31       asymmetric reagent with main group elements, transition metal and

1 lanthanide metals, polymer supported catalysis, nucleophilic  
2 displacement of fluorine atoms to modify characteristics of molecule,  
3 incorporation of molecule into crown ethers for development of  
4 phase transfer catalysts, use of compound as a monomer for  
5 polymerization, asymmetric polymer supported electrochemical  
6 oxidation catalysis, as a chiral auxiliary in an asymmetric reaction, as a  
7 resolving agent for chiral compounds, including but not limited to  
8 amines, asymmetric catalysis (reagent) in fluorous phase reactions, as a  
9 chiral stationary phase for HPLC and other chromatographic  
10 techniques, and phase transfer catalyst between organic, fluorous  
11 phase and alkali solutions.

12  
13 28. An asymmetric ligand comprising an aromatic ring system and at least  
14 one electronegative substituent, that is modified by selectively  
15 nucleophilically substituting at least one electronegative substituent  
16 with a nucleophile.

17  
18 29. A ligand as claimed in claim 28 wherein the aromatic ring system  
19 comprises a biphenyl, binaphthyl, bipyridine ring system or a  
20 derivative thereof.

21  
22 30. A ligand as claimed in claim 28 wherein the aromatic ring system is  
23 axially chiral.

24  
25 31. A ligand as claimed in claim 30 wherein the electrophilic substituent  
26 comprises fluorine.

27  
28 32. A ligand as claimed in claim 31 wherein the aromatic ring system  
29 comprises a biphenyl, binaphthyl or bipyridine ring system or a  
30 derivative thereof.

31

- 1 33. A ligand as claimed in claim 32 wherein the aromatic ring system  
2 comprises binaphthyl ring system or a derivative thereof.  
3
- 4 34. A ligand as claimed in any one of claims 28 to 33 comprising a  
5 nucleophile X, wherein X has the meaning defined in claim 16.  
6
- 7 35. A ligand as claimed in any one of claims 28 to 33 comprising a  
8 nucleophile wherein the nucleophile is hydroxy or C<sub>1</sub>-C<sub>6</sub> alkoxy.  
9
- 10 36. A ligand as claimed in claim 33 wherein a nucleophile is selectively  
11 substituted in the 7 and 7' positions.  
12
- 13 37. A ligand as claimed in claim 33 wherein a nucleophile is selectively  
14 substituted in the 7, 7', 6 and 6' positions.  
15
- 16 38. A ligand as claimed in claim 37 wherein the nucleophile substituted  
17 in the 7 and 7' positions is the same as the nucleophile substituted in  
18 the 6 and 6' positions.  
19
- 20 39. A ligand as claimed in claim 37 wherein the nucleophile substituted  
21 in the 7 and 7' positions is different from the nucleophile substituted  
22 in the 6 and 6' positions.  
23
- 24 40. A ligand as claimed in claim 27 wherein the binaphthyl ring system is  
25 a 2, 2' di-substituted binaphthyl ring system, and wherein the  
26 substituents at the 2 and 2' positions are the same or different and are  
27 each OR where R is as defined in claim 7.  
28
- 29 41. A ligand as claimed in claim 32 comprising a nucleophile X wherein X  
30 is as defined in claim 16.  
31

- 1 42. A ligand as claimed in claim 40 comprising a nucleophile wherein the  
2 nucleophile is hydroxy or C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkoxy.  
3
- 4 43. A ligand as claimed in claim 40 wherein a nucleophile is selectively  
5 substituted in the 7 and 7' positions on the binaphthyl ring system.  
6
- 7 44. A ligand as claimed in claim 40 wherein a nucleophile is selectively  
8 substituted in the 6 and 6' positions on the binaphthyl ring system.  
9
- 10 45. A ligand as claimed in claim 44 wherein the same nucleophile is  
11 selectively substituted in the 6, 6', 7 and 7' positions.  
12
- 13 46. A ligand as claimed in claim 44 wherein different nucleophiles are  
14 selectively substituted in the 7 and 7' positions and in the 6 and 6'  
15 positions.  
16
- 17 47. A method of generating a library of a predetermined number of  
asymmetric ligands comprising:  
18
- 19 a) Providing an aromatic ring system having at least one  
20 electronegative substituent;  
21
- 22 b) Selective substituting at least one electronegative substituent with  
a nucleophile; and  
23
- 24 c) Repeating steps a) and b) a predetermined number of times to  
obtain a predetermined number of ligands.  
25
- 26 48. The method as claimed in claim 47 wherein the same aromatic ring  
27 system is provided in each step a) and a different nucleophile is  
28 selectively substituted for at least one electronegative substituent in  
29 each step b).  
30

- 1 49. The method as claimed in claim 47 wherein the aromatic ring system  
2 provided in step a) is selected from benzene, pyridine, naphthalene,  
3 anthracene and their derivatives.  
4
- 5 50. The method as claimed in claim 48 wherein the aromatic ring system  
6 is axially chiral.  
7
- 8 51. The method as claimed in claim 50 wherein the aromatic ring system  
9 is selected from biphenyl, binaphthyl, bipyridine and derivatives  
10 thereof.  
11
- 12 52. The method as claimed in claim 51 wherein the aromatic ring system  
13 is a binaphthyl derivative.  
14
- 15 53. The method as claimed in 47 wherein the electronegative substituent  
16 is selected from the group of electronegative substituent consisting of  
17 fluorine, Cl, Br, I, CN and NO<sub>2</sub>.  
18
- 19 54. The method as claimed in claim 51 or 52 wherein the electronegative  
20 substituent is fluorine.  
21
- 22 55. The method as claimed in any one of claims 47 to 54 wherein the  
23 nucleophiles selectively substituted in steps b) are selected from the  
24 group of nucleophiles X, wherein X is as defined in claim 16.  
25
- 26 56. The method as claimed in any one of claims 47 to 54 wherein the  
27 nucleophiles selectively substituted in steps b) are selected from  
28 hydroxy, and C<sub>1</sub>-C<sub>6</sub> alkoxy.  
29

- 1 57. The method as claimed in claim 48 wherein in each step b) the  
2 nucleophile is selectively substituted in the same position on the  
3 aromatic ring system.  
4
- 5 58. The method as claimed in claim 48 wherein in each step b) the  
6 nucleophile is optionally selectively substituted in different positions.  
7
- 8 59. The use of a library of ligands made by a method as claimed in any one  
9 of claims 47 to 58 to screen the pharmacological activity of each ligand  
10 within the library.

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(54) Title: ASYMMETRIC LIGANDS HAVING USE AS CATALYSTS

(57) Abstract: Disclosed are electronically perturbed asymmetric aromatic ligands. In one aspect, the ligands are polyfluorinated. The ligands may be nucleophilically substituted. The ligands have many useful applications including catalytic applications. In a preferred aspect, the ligands are polyfluorinated binaphthyl ring derivatives, which are 2,2' dihydroxy or dialkoxy substituted.



6  
1  
1

6  
1  
1

## 1 WHAT IS CLAIMED IS:

2

3 1. An asymmetric ligand comprising an aromatic ring system that is  
4 polyfluorinated.

5

6 2. The ligand as claimed in claim 1 wherein the aromatic ring system in the  
7 form of a biphenyl, binaphthyl, bipyridal ring system, or a derivative  
8 thereof.

9

10 3. The ligand as claimed in claim 2 wherein the ligand is axially chiral due to  
11 steric hinderance.

12

13 4. The ligand as claimed in claim 2 wherein the aromatic ring system  
14 comprises a binaphthyl derivative.

15

16 5. The ligand as claimed in claim 4 wherein the aromatic ring system  
17 comprises a 2, 2' di substituted binaphthyl ring system.

18

19 6. The ligand as claimed in claim 5 wherein the aromatic ring system is a 2,  
20 2' di substituted binaphthyl ring system, and wherein the substituents at  
21 the 2 and 2' positions are the same or different, and are each OR where R  
22 may be:

23

a) Hydrogen; or

24

b) C<sub>1</sub>-C<sub>20</sub> aromatic, aliphatic, linear or branched, saturated or  
25 unsaturated, unsubstituted or substituted with:

26

i) N, O, S, or P;

27

ii) PR'R'' where R' and R'' are the same or different and are  
28 hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or  
29 branched, saturated or unsaturated, unsubstituted or  
30 substituted with N, O, S, or P;

31

iii) phosphine oxide;

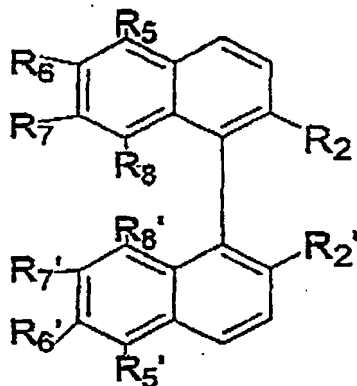


- 1 iv)  $NR''''$  where  $R'''$  and  $R''''$  are the same or different and  
2 are hydrogen, or  $C_1-C_{20}$  that may be aromatic, aliphatic,  
3 linear or branched, saturated or unsaturated, unsubstituted  
4 or substituted with N, O, S, or P;  
5 v)  $SR''''R''''$  where  $R''''$  and  $R''''$  are the same or different  
6 and are hydrogen, or  $C_1-C_{20}$  that may be aromatic, aliphatic,  
7 linear or branched, saturated or unsaturated, unsubstituted  
8 or substituted with N, O, S, or P.  
9
- 10 7. The ligand as claimed in claim 6 wherein R is hydrogen, or  $C_1-C_6$  alkyl  
11 which is linear or branched.  
12
- 13 8. The ligand as claimed in any one of claims 1 to 7 that is additionally  
14 substituted with chlorine.  
15
- 16 9. The ligand as claimed in claim 5 or 6 wherein the 5, 6, 7, and 8 positions  
17 of the binaphthyl ring system are fluorinated and the 5', 6', 7', and 8'  
18 positions of the binaphthyl ring system are not substituted with an  
19 electronegative radical.  
20
- 21 10. The ligand as claimed in claim 5 or 6 wherein the 5, 6, 7, and 8 positions  
22 of the binaphthyl ring system are not substituted with an electronegative  
23 radical, and the 5', 6', 7', and 8' positions of the binaphthyl ring system are  
24 fluorinated.  
25
- 26 11. The ligand as claimed in claim 4, 5, 6, or 7 wherein the binaphthyl ring  
27 system is fluorinated at the 5, 5', 6, 6', 7, 7', 8 and 8' positions.  
28
- 29 12. The ligand as claimed in claim 7 which is selected from the group of  
30 ligands comprising 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dihydroxy-1,1'-  
31 binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dimethoxy-1,1'-



binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-n-propoxy-1,1'-binaphthyl and 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-i-propoxy-1,1'-binaphthyl.

13. An asymmetric compound of the formula III:



wherein R2 and R2' are the same or different and are OR where R is:

- a) Hydrogen;
- b) C<sub>1</sub>-C<sub>20</sub> alkyl aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with:
  - i) N, O, S, or P;
  - ii) PR'R'' where R' and R'' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;
  - iii) phosphine oxide;
  - iv) NR'''R'''' where R''' and R'''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;
  - v) SR''''R''''' where R'''' and R''''' are the same or different and are hydrogen, or C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic,



- 1 linear or branched, saturated or unsaturated, unsubstituted  
2 or substituted with N, O, S, or P;  
3 vi) and R5, R5', R6, R6', R7, R7', R8 and R8' are independently  
4 hydrogen, fluorine, CN, or NO<sub>2</sub>, OR (where R is as defined  
5 above), SO<sub>2</sub>Ar where Ar is any aromatic ring system, SPh,  
6 Cl, Br, I, N<sub>3</sub>, NR<sub>3</sub><sup>+</sup> where each R is the same or different and  
7 may be as defined above, OAr where Ar is as defined above,  
8 SR where R is as defined above, NH<sub>2</sub>, a nucleophile X,  
9 wherein X may be OR<sub>9</sub>, NR<sub>10</sub>R<sub>11</sub>, SR<sub>12</sub>, SiR<sub>13</sub>R<sub>14</sub>R<sub>15</sub>,  
10 SeR<sub>16</sub> and wherein each of R<sub>9</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>,  
11 R<sub>15</sub> and R<sub>16</sub> is the same or different and may be hydrogen,  
12 C<sub>1</sub>-C<sub>20</sub> that may be aromatic, aliphatic, linear or branched,  
13 saturated or unsaturated, unsubstituted or substituted with  
14 N, O, S, or P;  
15 vii) with the proviso that more than two of R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>7</sub>,  
16 R<sub>7'</sub>, R<sub>8</sub> and R<sub>8'</sub> is fluorine.  
17

- 18 14. The compound as claimed in claim 13 wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are the  
19 same and are H or F, and R<sub>5'</sub>, R<sub>6'</sub>, R<sub>7'</sub> and R<sub>8'</sub> are the same and are  
20 different than R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>.  
21  
22 15. The compound as claimed in claim 13 wherein R<sub>2</sub> and R<sub>2'</sub> are the same  
23 or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or branched, and  
24 R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>7</sub>, R<sub>7'</sub>, R<sub>8</sub> and R<sub>8'</sub> are each fluorine.  
25  
26 16. The compound as claimed in claim 13 wherein R<sub>2</sub> and R<sub>2'</sub> are the same  
27 or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or branched, and  
28 R<sub>5</sub>, R<sub>5'</sub>, R<sub>6</sub>, R<sub>6'</sub>, R<sub>8</sub> and R<sub>8'</sub> are each fluorine, and R<sub>7</sub> and R<sub>7'</sub> are the  
29 same or different and are a nucleophile X as claimed in claim 13.  
30



- 1 17. The compound as claimed in claim 13 wherein R2 and R2' are the same  
2 or different and are hydrogen or C<sub>1</sub>-C<sub>6</sub> aliphatic, linear or branched, and  
3 R5, R5', R8 and R8' are each fluorine, and R6, R6', R7, R7' are the same  
4 or different and are a nucleophile X as claimed in claim 13.  
5
- 6 18. The compound as claimed in claim 16 or 17 wherein the nucleophile X is  
7 hydroxy or C<sub>1</sub>-C<sub>6</sub> alkoxy.  
8
- 9 19. A modified asymmetric polyfluorinated binaphthyl based ligand wherein  
10 the fluorine atom in at least one of positions 5 and 5', 6 and 6', 7 and 7',  
11 and 8 and 8' is selectively displaced with a nucleophile.  
12
- 13 20. The modified polyfluorinated binaphthyl based ligand as claimed in claim  
14 19 wherein the fluorine atoms at positions 7 and 7' are selectively  
15 displaced with a nucleophile.  
16
- 17 21. The modified polyfluorinated binaphthyl based ligand as claimed in claim  
18 20 wherein the fluorine atoms at positions 6, 6', 7 and 7' are selectively  
19 displaced with a nucleophile.  
20
- 21 22. A ligand as claimed in any one of claims 1 to 21 wherein the ligand is  
22 linked to a solid support.  
23
- 24 23. A ligand as claimed in any one of claims 1 to 21 wherein the ligand is  
25 linked to an electrode surface.  
26
- 27 24. The use a ligand as claimed in any one of claims 1 to 23 for an application  
28 selected from the group consisting of asymmetric catalysis with main  
29 group elements, transition metal and lanthanide metals, asymmetric  
30 reagent with main group elements, transition metal and lanthanide metals,  
31 polymer supported catalysis, nucleophilic displacement of fluorine atoms



- 1 to modify characteristics of molecule, incorporation of molecule into crown  
2 ethers for development of phase transfer catalysts, use of compound as a  
3 monomer for polymerization, asymmetric polymer supported  
4 electrochemical oxidation catalysis, as a chiral auxiliary in an asymmetric  
5 reaction, as a resolving agent for chiral compounds, including but not  
6 limited to amines, asymmetric catalysis (reagent) in fluorous phase  
7 reactions, as a chiral stationary phase for HPLC and other  
8 chromatographic techniques, and phase transfer catalyst between  
9 organic, fluorous phase and alkali solutions.
- 10
- 11 25. An asymmetric ligand comprising an aromatic ring system that is  
12 polyfluorinated, that is modified by selectively nucleophilically substituting  
13 at least one fluorine atom with a nucleophile.
- 14
- 15 26. A ligand as claimed in claim 25 wherein the aromatic ring system  
16 comprises a biphenyl, binaphthyl, bipyridine ring system or a derivative  
17 thereof.
- 18
- 19 27. A ligand as claimed in claim 25 wherein the aromatic ring system is axially  
20 chiral.
- 21
- 22 28. A ligand as claimed in claim 27 wherein the aromatic ring system  
23 comprises binaphthyl ring system or a derivative thereof.
- 24
- 25 29. A ligand as claimed in any one of claims 25 to 28 comprising a nucleophile  
26 X, wherein X has the meaning defined in claim 13.
- 27
- 28 30. A ligand as claimed in any one of claims 25 to 28 comprising a nucleophile  
29 wherein the nucleophile is hydroxy or C<sub>1</sub>-C<sub>6</sub> alkoxy.
- 30



- 1 31. A ligand as claimed in claim 28 wherein a nucleophile is selectively  
2 substituted in the 7 and 7' positions.  
3
- 4 32. A ligand as claimed in claim 28 wherein a nucleophile is selectively  
5 substituted in the 7, 7', 6 and 6' positions.  
6
- 7 33. A ligand as claimed in claim 32 wherein the nucleophile substituted in the  
8 7 and 7' positions is the same as the nucleophile substituted in the 6 and  
9 6' positions.  
10
- 11 34. A ligand as claimed in claim 32 wherein the nucleophile substituted in the  
12 7 and 7' positions is different from the nucleophile substituted in the 6 and  
13 6' positions.  
14
- 15 35. A ligand as claimed in claim 32 wherein the binaphthyl ring system is a 2,  
16 2' di-substituted binaphthyl ring system, and wherein the substituents at  
17 the 2 and 2' positions are the same or different and are each OR where R  
18 is as defined in claim 6.  
19
- 20 36. A ligand as claimed in claim 35 comprising a nucleophile wherein the  
21 nucleophile is hydroxy or C<sub>1</sub>-C<sub>6</sub> branched or straight chain alkoxy.  
22
- 23 37. A ligand as claimed in claim 35 wherein a nucleophile is selectively  
24 substituted in the 7 and 7' positions on the binaphthyl ring system.  
25
- 26 38. A ligand as claimed in claim 35 wherein a nucleophile is selectively  
27 substituted in the 6 and 6' positions on the binaphthyl ring system.  
28
- 29 39. A ligand as claimed in claim 38 wherein the same nucleophile is  
30 selectively substituted in the 6, 6', 7 and 7' positions.  
31



- 1 40. A ligand as claimed in claim 38 wherein different nucleophiles are  
2 selectively substituted in the 7 and 7' positions and in the 6 and 6'  
3 positions.  
4
- 5 41. A method of generating a library of a predetermined number of  
6 asymmetric ligands comprising:  
7 a) Providing an asymmetric polyfluorinated aromatic ring system;  
8 b) Selective substituting at least one fluorine atom with a nucleophile;  
9 and  
10 c) Repeating steps a) and b) a predetermined number of times to  
11 obtain a predetermined number of ligands.  
12
- 13 42. The method as claimed in claim 41 wherein the aromatic ring system is  
14 axially chiral.  
15
- 16 43. The method as claimed in claim 42 wherein the aromatic ring system is  
17 selected from biphenyl, binaphthyl, bipyridine and derivatives thereof.  
18
- 19 44. The method as claimed in claim 43 wherein the same aromatic ring  
20 system is provided in each step a) and a different nucleophile is  
21 selectively substituted for at least one fluorine atom in each step b).  
22
- 23 45. The method as claimed in claim 43 wherein the aromatic ring system is a  
24 binaphthyl derivative.  
25
- 26 46. The method as claimed in any one of claims 41 to 45 wherein the  
27 nucleophiles selectively substituted in steps b) are selected from the group  
28 of nucleophiles X, wherein X is as defined in claim 13.  
29

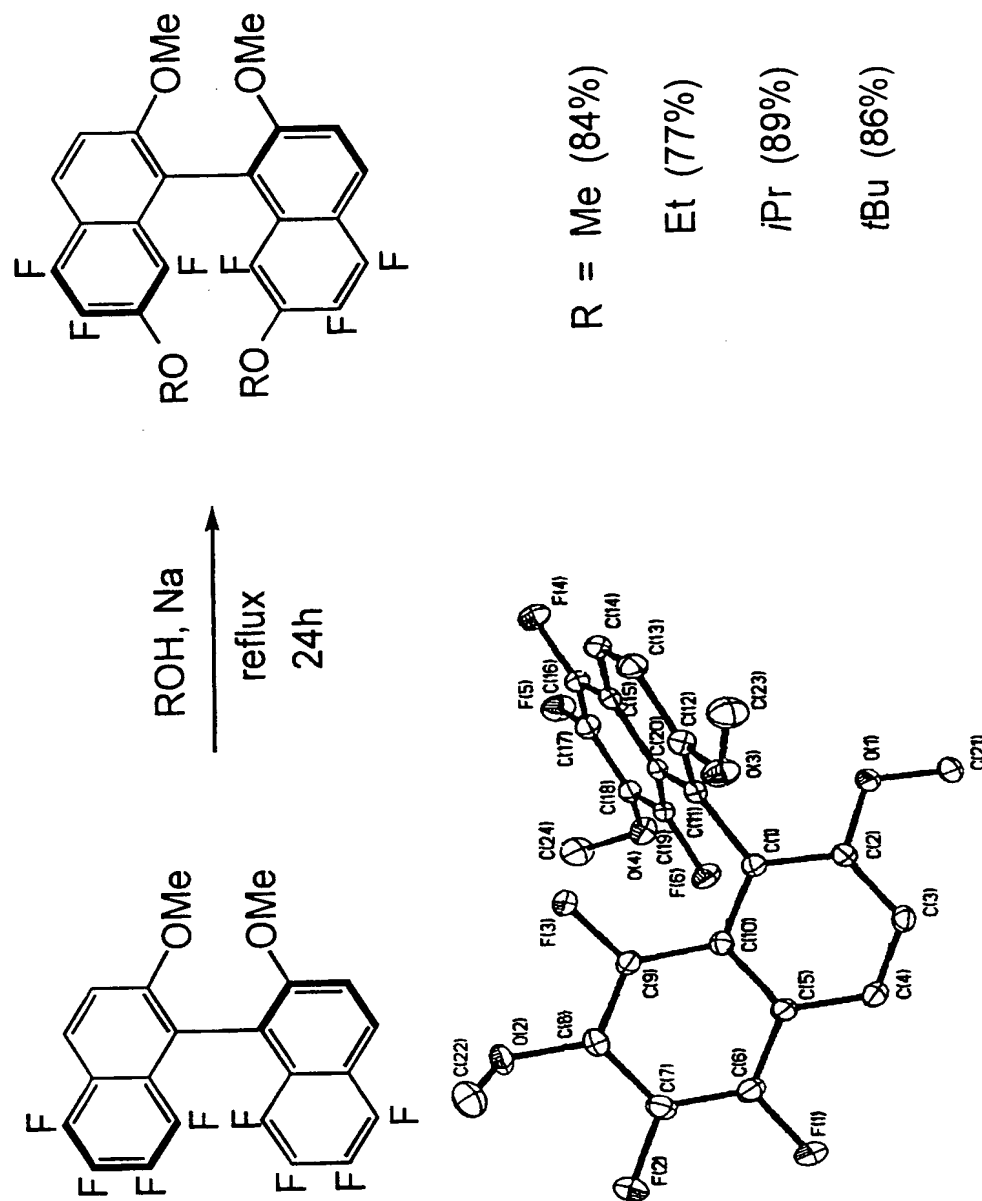


- 1 47. The method as claimed in any one of claims 41 to 45 wherein the  
2 nucleophiles selectively substituted in steps b) are selected from hydroxy,  
3 and C<sub>1</sub>-C<sub>6</sub> alkoxy.  
4
- 5 48. The method as claimed in claim 44 wherein in each step b) the  
6 nucleophile is selectively substituted in the same position on the aromatic  
7 ring system.  
8
- 9 49. The method as claimed in claim 44 wherein in each step b) the  
10 nucleophile is optionally selectively substituted in different positions.  
11
- 12 50. The use of a library of ligands made by a method as claimed in any one of  
13 claims 41 to 49 to screen the pharmacological activity of each ligand  
14 within the library.



1/10

Figure 1

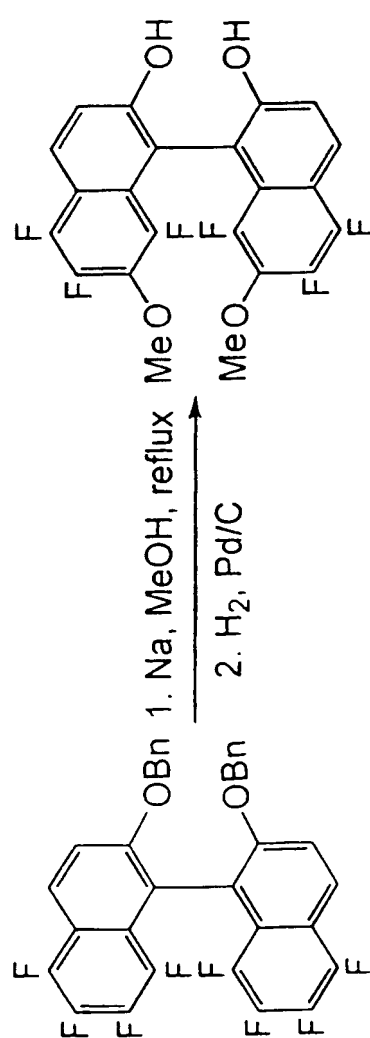


Molecular structure of the 7,7'-bis(methoxy) adduct

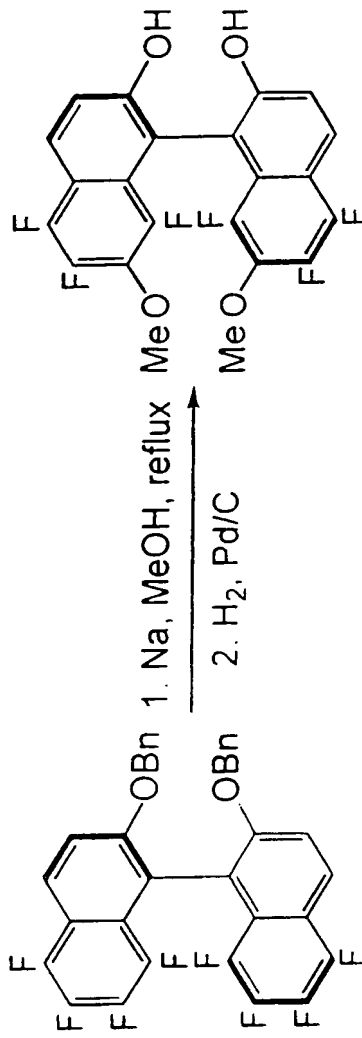


2/10

Figure 2

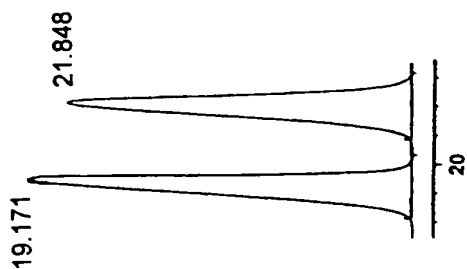


racemic

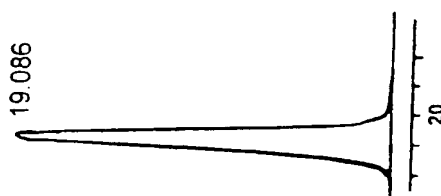


R (99% ee)

R (99% ee)



Chiralcel OD

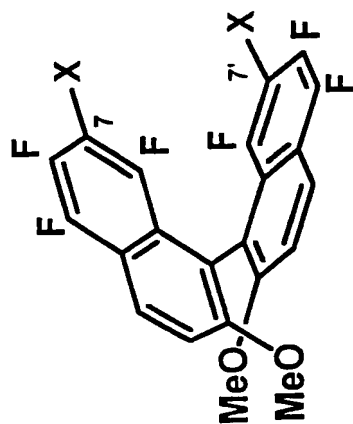


Chiralcel OD



3/10

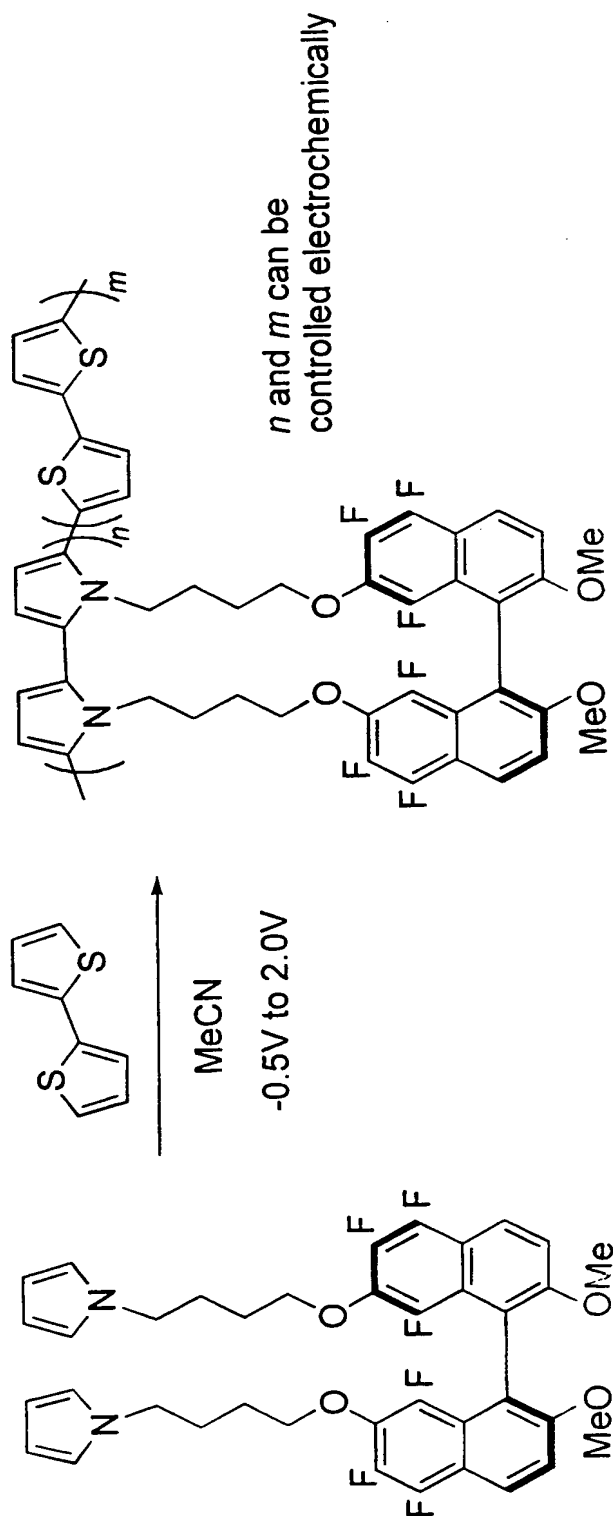
Figure 3





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Figure 4





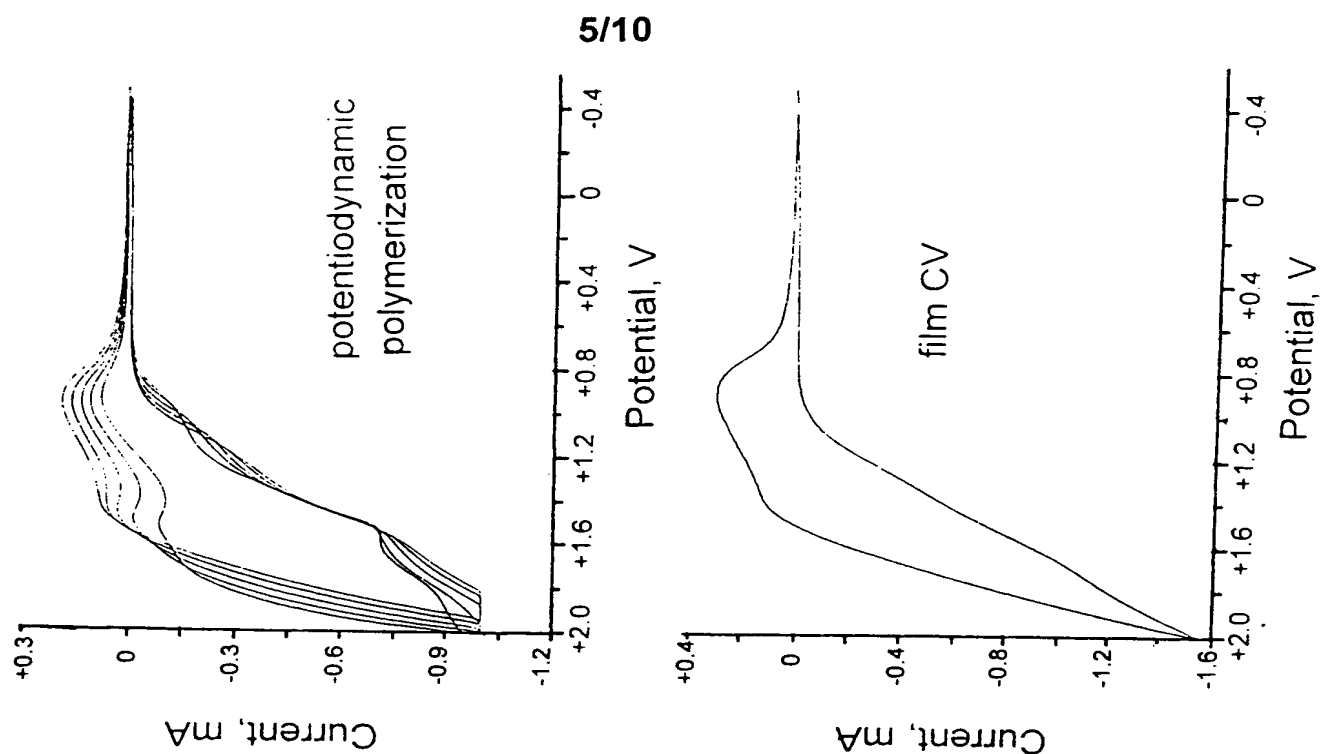
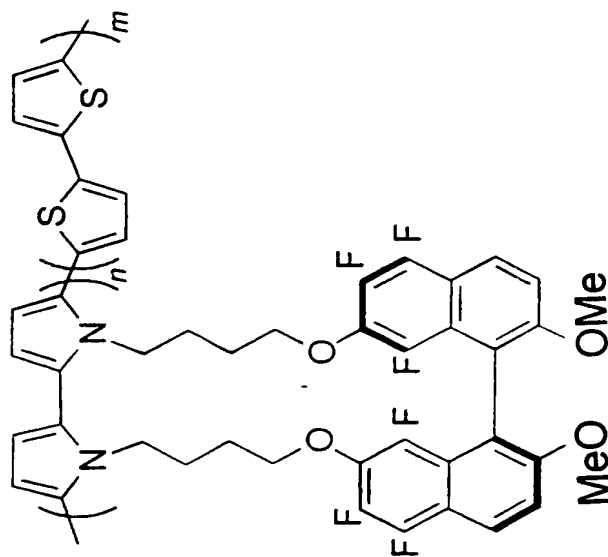


Figure 5

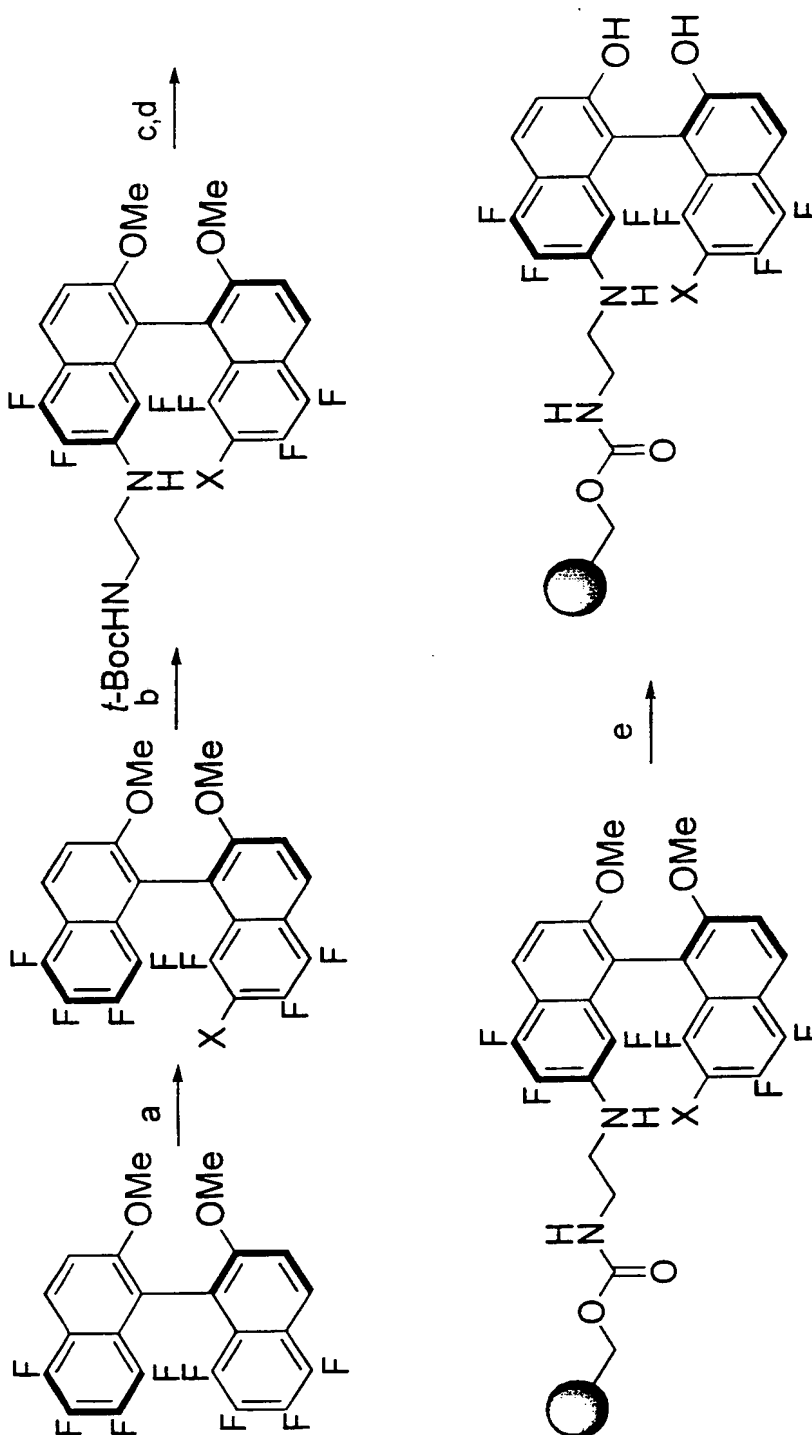


pyrrole/bithiophene  
feed ratio: 2:1



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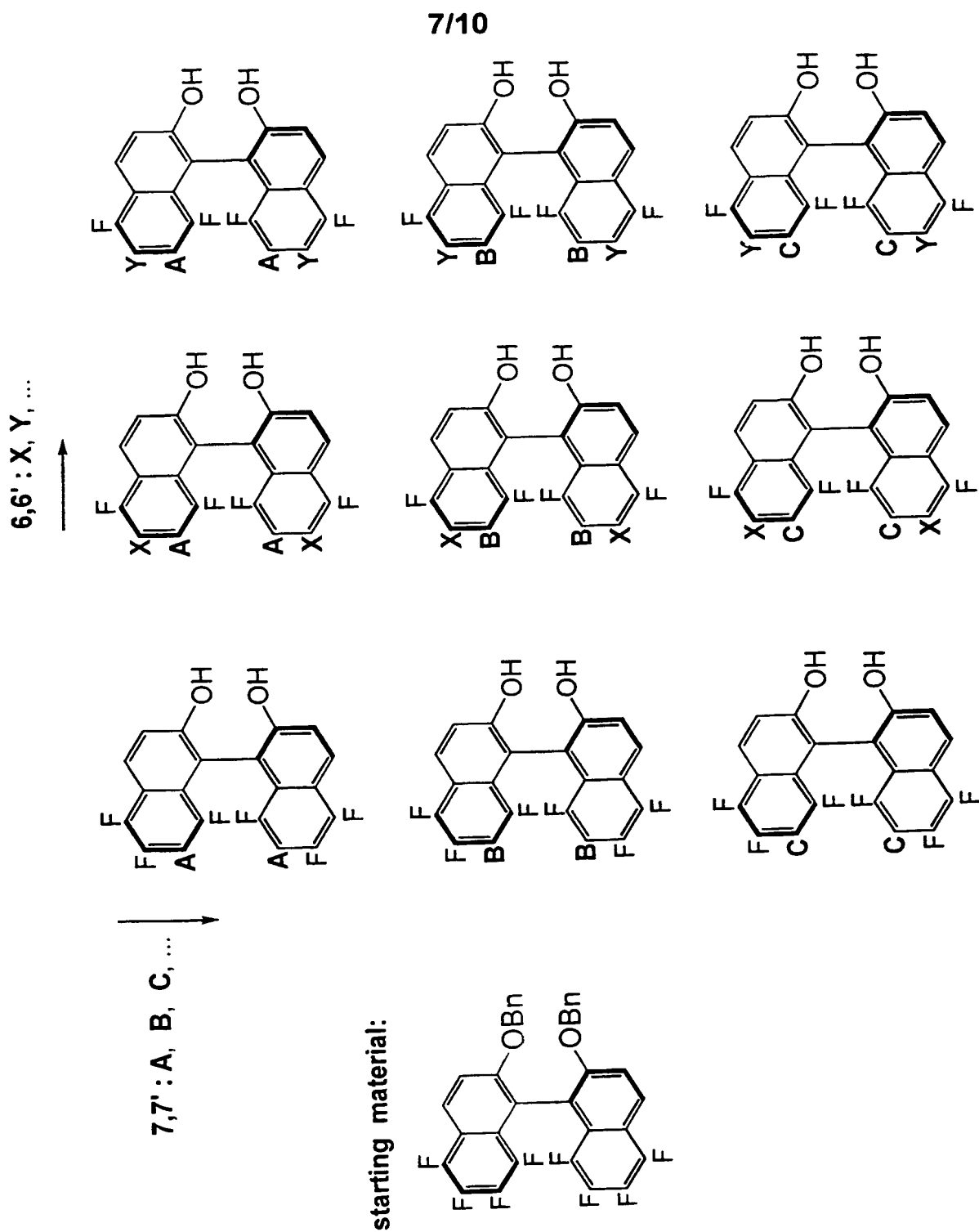
Figure 6



Key: a. XH (1 eq), toluene, 100 °C; b. NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH(*t*-Boc), toluene, 100 °C; c. TFA, DCM;  
 d. CDI, THF, TentaGel S OH; e. Pd-C, HCOONH<sub>4</sub>, MeOH, reflux



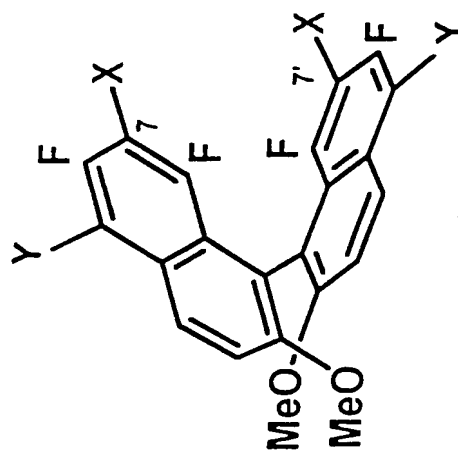
Figure 7





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Figure 8





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Figure 9

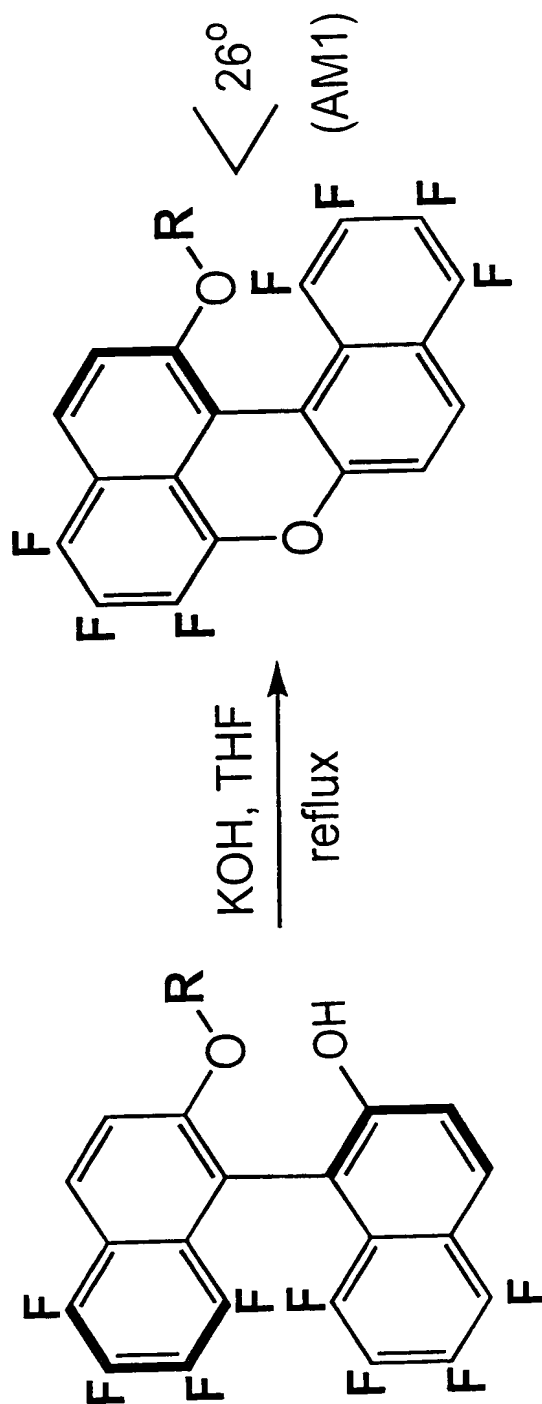




Figure 10

